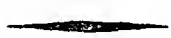




# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CXXXIII



A STUDY OF INFECTIOUS MONONUCLEOSIS  
(PFEIFFER'S DISEASE) FROM THE  
ETIOLOGICAL POINT OF VIEW

BY

*PER J. WISING*

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TRYCKERI AKTIEBOLAGET THULE, STOCKHOLM 1942



# ACTA MEDICA SCANDINAVICA

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FROM THE MEDICAL CLINIC OF KAROLINSKA SJUKHUSET (PROFESSOR  
N. SVARTZ) AND THE STATE BACTERIOLOGICAL LABORATORY  
(PROFESSOR C. KLING), STOCKHOLM.

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# A Study of Infectious Mononucleosis (Pfeiffer's Disease) from the Etiological Point of View

by

PER J. WISING

ACTA MEDICA SCANDINAVICA  
SUPPLEMENTUM CXXXIII

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# PREFACE

The present study was carried out with the hope of throwing some light on the problem of the etiology of infectious mononucleosis. A number of experiments were carried out in an attempt to discover whether the opinion of NYFELDT and others as to the bacterial genesis of the disease could be confirmed. Attempts were also made to transfer infectious mononucleosis to rabbits, monkeys and man. Finally a study was made of the histopathology of the lymph nodes during the acute stage of the disease whereby stained sections as well as photomicrographs of unstained tissue at the absorption maximum of nucleic acid in ultraviolet light were examined.

My investigations were carried out at the First Medical Clinic of the Royal Seraphimer Hospital, the Medical Clinic of Karolinska Sjukhuset (Karolinska Hospital) and the State Bacteriological Laboratory, Stockholm. To the heads of these institutions, Professors N. SVARTZ and C. KLING, I owe a debt of deep gratitude for facilitating my work, for valuable advice and support, as well as for their great interest during the course of my experiments.

My very warm thanks are also due Professors F. HENSCHEN and O. REUTERWALL, Dr L. SANTESSON and Dr Å. LINDGREN for valuable advice and help given me in the examination of certain microscopical sections.

I particularly want to thank my friends Dr E. WASSÉN for valuable advice in the fields of bacteriology and Dr T. CASPERSSON, Lecturer in Medical Physics at the Karolinska Institute, for his kind and friendly help in the preparation and interpretation of the photomicrographs in ultraviolet light. I want to express my very warm thanks to Dr AAGE NYFELDT for sending me his *Listerella* strains.

It is also my pleasant duty to express thanks to Professors G. HOLMGREN, H. BERGLUND, T. SKOOG, Chief Physicians E. B.

SALÉN, R. BERGMAN, N. RAIIM and other colleagues for the infectious mononucleosis cases they have kindly placed at my disposal.

Finally my thanks are due to the Swedish Society for Medical Research which by financial support made the present investigations possible.

Stockholm april 1942.

*Per J. Wising.*

# I. INTRODUCTION

## A. THE CLINICAL HISTORY OF INFECTIOUS MONONUCLEOSIS.

IT IS AT PRESENT possible to define glandular fever, infectious mononucleosis, or Pfeiffer's disease, as an acute, contagious, not infrequently epidemic, infectious disease *sui generis*, in all probability caused by a specific, hitherto unknown, pathogenic agent. The disease is characterized by fever, a general reaction of the lymphatic system with enlargement of the lymph nodes, often particularly striking in the cervical region, a characteristic "lymphatic" blood picture, the development of specific heterophilic antibodies in the serum, generally an intense angina, not infrequently enlargement of the spleen, occasionally conjunctivitis, a roseolar rash, hematuria, enlargement of the liver, icterus and in exceptional cases symptoms of meningitis or meningo-encephalitis. This condition which was originally described as a children's disease spares no age but is by far the most common under 30 years of age. On the whole the prognosis can be described as very good in that only a few fatal cases have so far been reported despite the relative frequency of the disease.

The former of the two names under which the disease is nowadays known is derived from PFEIFFER who was the first to describe it as glandular fever (*Drüsenfieber*). The later designation, infectious mononucleosis, was introduced by SPRUNT & EVANS who did not recognize that a number of cases reported by them were identical with Pfeiffer's disease. Though perhaps preference ought to be given to PFEIFFER's original title, glandular fever, both names are at present in common use, infectious mononucleosis showing exclusive predominance in American literature. Since infectious mononucleosis is the only term used in this country, it will be solely used in the following.

The recognition of infectious mononucleosis as a clinical entity has a history of its own of considerable interest, related in detail in



exemplary manner in the works of LEHNDORFF & SCHWARZ, GLANZMANN and TIDY. The following short survey is to some extent based on the publications of the authors mentioned.

Although, in 1885 in a textbook on Diseases of Children under the heading "Idiopatische LymphdrüSENSCHWELLUNG" FILATOW describes a number of cases which probably suffered from infectious mononucleosis, we must nevertheless ascribe to the keen clinical perception of EMIL PFEIFFER the honour of distinguishing as a characteristic entity the cases of infectious mononucleosis from the mass of infectious conditions with swelling of the lymph nodes of the neck. PFEIFFER presented this now classical material at the Congress of Natural Sciences in Cologne in 1889. He described the lymph node enlargement and the enlargement of the liver and spleen as well as the sometimes epidemic occurrence, but he was not acquainted with the peculiar blood picture. He received at once the endorsement of his colleagues who reported observations on similar cases and during the last decade of the nineteenth century there prevailed a lively interest in the clinical aspect of the condition. At the conclusion of Pfeiffer's lecture HEUBNER pointed out the occurrence of hematuria as a complication. In 1890 RAUCHFUSS and VON STARCK verified these observations and in 1891 PROTASSOW laid stress upon the occurrence of conjunctivitis and an eruption. In 1894 DESPLATS gave an account of cases with general lymph node enlargement and that same year HOERSCHELMANN emphasized the frequency of an angina in infectious mononucleosis. KORSAKOFF reported the occurrence of this disease in siblings one of which showed only lymph node enlargement while the others had an angina as well. The first large epidemic was described by PARK WEST in 1896 in the United States of America. THORNTON, DURNO, BYERS, WILLIAMS, BELLOTTI, FEDELE and others contributed around the turn of the century with further statistical reports.

From 1900 to 1920 the Pfeiffer disease picture seems to have fallen into relative oblivion. Only some few records of observed cases are to be found in the literature from this period and a number of workers such as COMBY, HOCHSINGER, TRAUTMANN, SCHLEISSNER even questioned altogether the existence of the disease. Perhaps correct is GLANZMANN's assumption, that infective mononucleosis had disappeared on the continent during this period (LEHNDORFF & SCHWARZ).

CURSCHEMANN in 1906 was the first to report a differential blood count on a case of infectious mononucleosis which he however interpreted as atypical epidemic parotitis, a still not unusual diagnostic mistake. The peculiar "lymphoid" blood picture would seem to have first come to the attention of TÜRK in 1907. He then described two typical cases under the heading "Septische Erkrankung mit Verkümmern des Granulocytensystems". Türk expressed particularly his surprise at the rapid recovery and believed that the disease picture observed might be due to some kind of subleukemic lymphomatosis. In 1913 MARCHAND described a similar case and suggested that it might be a question of an until then unknown specific disease. The same year CANOT discussed "the lymphocytosis of infection" and in 1918 DEUSSING referred to "Diphtherieähnliche Anginen mit lymphatischer Reaktion".

In 1920 SPRUNT & EVANS described a number of typical cases, using for the first time the term "Infectious Mononucleosis". The next year LETHBRIDGE TIDY & MORLEY recorded the first case diagnosed as glandular fever in which the presence of lymphocytosis was recognized and after reading SPRUNT & EVANS article they were satisfied that the two groups were of the same origin. They considered that the disease had to be accepted as an acute infection, as a general and not merely a local infection and as a clinical entity *sui generis*. This conception was soon widely accepted and in 1928 CHEVALLIER and ÉMIL SCHWARZ emphasized that the Monocytenangina of SCHULTZ, the Lymphoblastenangina of PREUSS, the Lymphatic Reaction of BROGSITTER, the Acute Lymphadenosis with Lymphocytosis of DOWNEY & MCKINLEY as well as a number of cases described as benign convalescing leukemias (JACKSON & SMITH, IRELAND and collaborators, EASON among others) all provided only clinical variations of the same "Maladie de Pfeiffer et de Türk", as Chevallier termed it.

The decisive support for the correctness of this conception has been provided by the serological investigations of recent years. During the period 1924 to 1930 HAGANUTZIG, DEICHER, TANIGUCHI, DAVIDSOHN among others demonstrated the occurrence of Forssman antibodies in increased quantity in the serum from persons who had received injections of horse serum or were suffering from serum disease. PAUL & BUNNELL in 1932 investigated in this connection a large hospital material in regard to the occurrence of immune sub-

stances with an agglutinating and haemolytic action on sheep red blood cells and found that infectious mononucleosis was apparently the only additional condition in which such could be demonstrated in any great quantity. Independently of one another VON MOERS-MESMER, STUART and collaborators, DAVIDSOHN, BAILEY & RAFFEL have further shown that these heterophilic antibodies in the serum from infectious mononucleosis patients are not identical with the Forssman antibodies and that they in all probability are specific for the disease. The extraordinary value of the Paul & Bunnell hetero-agglutination reaction for the diagnosis of infectious mononucleosis has been established in a large number of papers during the last years. In Scandinavia investigations in this field have been reported by OLESEN, BANG and KRISTENSEN, RUDEBECK, WISING, HELLAND-HANSEN and THOMSEN among others.

## B. PREVIOUS OPINIONS AND INVESTIGATIONS ON THE ETIOLOGY.

Although in previous decades the symptom complex of infectious mononucleosis was interpreted by many workers as evidence of the individual's specific mode of reaction to various infections of the upper respiratory tract (LABBÉ, GALLOIS, DELCOURT, FINKELSTEIN, FISCHL), to sepsis (CABOT, MARCHAND) or to an intestinal intoxication (v. STARCK, TRAUTMANN, HOCHSINGER), others understood that it must be a question of an infectious disease *sui generis* and searched for its etiological origin. Numerous attempts have thus been made to demonstrate the existence of a pathogenic agent in the blood, lymph nodes, tonsils, urine and salivary secretion from patients with infectious mononucleosis. Surveys of these investigations which predominantly deal with conditions in isolated or a few cases of the disease are included in the monographs of LEINDORFF & SCHWARZ and of NYFELDT both of 1932. Though common to all reports of positive results of cultivation on artificial substrates as to the cause of the disease has been the constant failure of other workers to be able to repeat the experiments, a brief summary of previous views and investigations on the subject would seem to be of some interest.

A large number of investigations of the bacterial flora in tonsillar swabs and in pharyngeal or nasal secretions have been reported. The

findings have been the common polymorphous picture of oral-pharyngeal flora with cocci, hemolytic and non-hemolytic, in clumps, diploid or chain arrangement, bacilli, fusiform bacilli and spirochaetes, without the demonstration of the predominance of any particular type of microorganism (LEHNDORFF). One of the most usual assumptions has been that infectious mononucleosis might be a streptococcus disease (KORSAKOFF, LUBLINSKI, COMBY and COLEMAN among others). SCHEER and KORSAKOFF each reported that they found streptococci in the urine in one such case. SCHMIDTHEINY obtained hemolytic streptococci on cultivation of the duodenal juice from one case.

Diphtheroid bacilli were discovered in the flora of the throat and in juice pressed from the lymph nodes in some cases reported by BALDRIDGE, ROHNER & HANSMANN and COON & THEWLISS. With the exception of the case published by the latter authors these organisms were always non-pathogenic when tested on animals. Genuine diphtheria bacilli have been observed on isolated occasions in cases with severe pseudomembranous lesions in the throat without it being possible however to ascribe to them any pathogenetic significance (HRABOWSKY, GLANZMANN, LEHNDORFF).

FRIEDEMANN & ELKELES assumed that the mononucleosis could be a general reaction from the lymphatic system to a generalized fusospirochilosis. Even BLOEDORN & HUGHTON and ZIKOWSKY believed in the significance of this symbiotic flora for the disease. BALDRIDGE and collaborators who also found the Vincent organisms in a number of cases point out however the prevalence of these in the oral and pharyngeal flora in all kinds of other conditions and deny them naturally any etiological connection with infectious mononucleosis. GORHAM, SMITH & HUNT reported the presence of spirochaetes on dark field examination of the blood in a number of patients with infectious mononucleosis. BALDRIDGE and his co-workers searched in vain for spirochaetes in the blood and in juice from the lymph nodes.

Numerous workers have made blood cultures. The results have always been negative or insignificant. In a number of cases the injection of blood and lymph node suspension into guinea-pigs and rabbits has given constantly negative results (BALDRIDGE among others). Tubercle bacilli have never been demonstrated.

In view of the apparent impossibility of transferring the disease

to the ordinary small laboratory animals and with the leukemias in mind, CHEVALLIER injected blood and lymph node suspension into chickens but the results were unfortunately negative. Like CHEVALLIER a number of researchers such as DOWNEY & STASNEY, GLANZMANN, DE BRUIN, THOMSEN & VIMTRUP have recently on purely clinical grounds expressed the opinion that the disease can probably be assumed to be caused by a virus with a specific lymphotropic affinity. The present author reported preliminarily in 1938 a number of results which could possibly be regarded as supporting such a conception. Macacus monkeys inoculated with a lymph node suspension, sterile on aerobic and anaerobic cultivation, fell ill in two cases with symptoms similar to those in human infectious mononucleosis. VAN DEN BERGHE & LIESSENS in 1939 reported that they had been able to pass a filtrable virus from a patient to a monkey. The description of the case of these latter workers reveals however that the patient can scarcely have been suffering from infectious mononucleosis for the blood picture was not typical.

Of the investigations published in recent years those of two particular workers have attracted special attention. In 1929 AAGE NYFELDT reported that he had found the cause of the disease in a particular diphtheroid organism which he called *Bacterium*, afterwards *Listerella monocytogenes hominis*. Since his first brief report in 1929 NYFELDT has published a further number of cases of infectious mononucleosis from which he reports *Listerella hominis* to have been cultivated. In 1937 he described the finding of this bacterium in blood cultures from 3 of 10 cases examined. A visible growth appeared after 12 to 14 days incubation at 37° C on peptone broth (Chapoteau-peptone). In 1937 in one case a growth of *Listerella* was obtained on liver and "Vita" bouillon after 3 to 4 days. Already after 24 hours however the substrate also contained profuse numbers of large Gram-positive motile rods. In 1938 growth of *Listerella* was obtained after 6 to 11 days from 4 out of 5 spinal fluids from cases of infectious mononucleosis with mild meningeal symptoms. Moreover in two of the latter cases broth cultures which had been inoculated with blood which had been kept up to three days in the laboratory at 25° C were positive on the 4th to the 6th day. In support of his assumption as to the pathogenic significance of the bacteria found, NYFELDT mentions that they in one case were agglutinated by the patient's serum in the dilution 1:250

and in another case in the dilution 1:3200, a not particularly convincing argument in view of the fact demonstrated by BERGSTRAND that saprophytic diphtheroids may give specific agglutination with homologous serum. Nothing is stated in regard to controls or in regard to the result of eventual examination as to the occurrence of agglutinins for the strains found in the remaining six cases.

NYFELDT inoculated into rabbits the strains he had cultivated intravenously and for this animal they proved pathogenic. The animals developed a leucocytosis and in a number of cases a simultaneous relative neutropenia. Monocytoid cells with bizarre nuclei appeared. The lymph nodes and spleen seem to have shown the changes typical of an acute infection. On the basis of these animal experiments NYFELDT draws extensive conclusions as well as parallels with conditions in a septic rabbit disease described by MURRAY, WEBB & SWANN and characterized among other things by a mononuclear blood picture. The normal markedly varying and difficultly evaluated blood picture in rabbits would seem a priori scarcely inviting for parallels on such a basis. The striking differences between the clinical and pathological picture in the disease produced by MURRAY, WEBB & SWANN with *Bacterium monocytogenes cuniculi* in young rabbits and infectious mononucleosis in man would also seem to justify the emphatic utterance of LEHNDORFF & KOVACS to the effect "dass wir mit Sicherheit sagen können, dass hier etwas prinzipiell Andersartiges vorliegt". Up to the present to the writer's knowledge no investigation has been published which satisfactorily supports NYFELDT's conception of the etiology of infectious mononucleosis.

During 1930 and 31 JOHN BLAND reported the result of a number of animal experiments which also seem to require mention. By inoculation of citrated blood from a human case of infectious mononucleosis BLAND produced in rabbits a fatal disease which he was able to pass on indefinitely. This disease differed in no way clinically or pathologically from the disease which could be produced by inoculation of a strain of *Toxoplasma cuniculi* of rabbit origin, including the presence of *Toxoplasms* in the organs of the infected animals. When blood from these rabbits was inoculated into a number of monkeys it produced a disease which showed certain similarities to human infectious mononucleosis with regard to the blood picture. However, in view of the clinical differences and also the

common occurrence of nosocomical protozoal infections in rabbits, Bland's assumption of the significance of his Toxoplasms for the etiology of human infectious mononucleosis can scarcely be accepted until confirmed from other quarters.

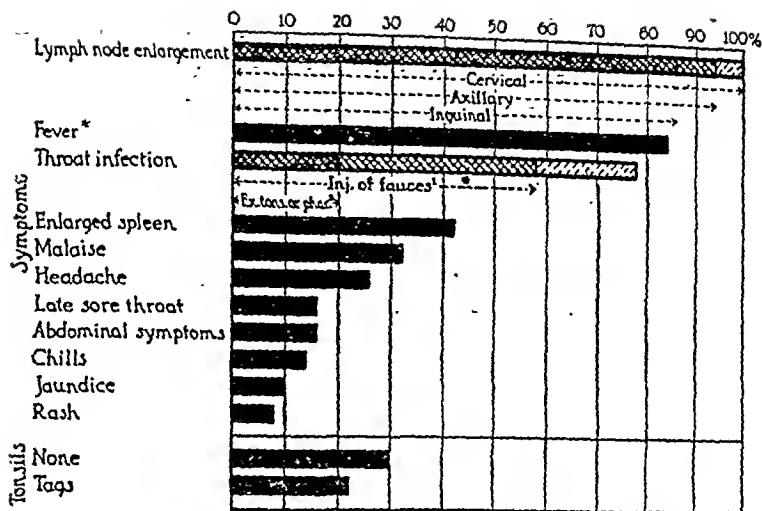
The results of NYFELDT as well as those of BLAND will be the object of further discussion in the following.

## II. THE INVESTIGATIONS OF THE AUTHOR

### I. Material and relevant clinical data.

The present experiments have been based on a series of 27 clinically, haematologically and serologically typical cases of infectious mononucleosis. All have been sporadic cases which have been taken care of in different hospitals in Stockholm during the period from December 1937 until January 1942 and the writer has had the advantage of examining and following them extensively thanks to the courtesy of the colleagues in question. The material is selected to the extent that, of the cases observed during the period in question, only those have been included, which have been under the writer's observation during the entire course of the disease including the initial stage of fever. Blood cultures have been made, the extirpated lymph nodes have been examined bacteriologically and pathologically and injection experiments on animals have been carried out with material from the patients. In addition a number of serobacteriological experiments have been performed on patients, healthy controls and experimental animals, with two *Listerella* strains obtained from NYFELDT. For various reasons the investigations on the individual patient have sometimes had to be limited. The disease is in the majority of cases a peculiarly benign condition and the initial fever stage is often of only a few days duration. When during the more or less afebrile convalescent period it seemed a priori as if the cultivation of the blood and of extirpated lymph nodes would offer little chance of positive results, such procedures were carried out only in cases where the diagnosis had been made at such an early stage that the investigation could be done while the patient was still febrile. Thus it has sometimes been the rapid regression of the disease which has prevented the carrying out of a specific procedure. In a number of other cases the sur-





\* Average duration: 10.8 days <sup>1</sup>Injection of fauces <sup>2</sup>Erosive tonsillitis or pharyngitis

Fig. 1. Outstanding symptoms and physical signs in order of frequency in fifty cases (thirty-eight male, twelve female) of infectious mononucleosis. (cit. by Mc Kinley).

gical topography of the lymphoma in question has counterindicated the taking of a biopsy, as have cosmetic considerations in a couple of other instances. In a few cases economic reasons have necessitated discharge of the patient from hospital before the completion of all the planned examinations.

The disease picture of infectious mononucleosis presents a multiplicity of clinical aspects. On the whole it is the picture of an acute infectious disease. Certain symptoms however often dominate the course of the disease to such an extent that they more or less impress a particular character on the case. Since long ago a distinction has been made between on the one hand the PFEIFFER type characterized by the more or less general lymph node enlargement where often particularly the cervical adenitis is of striking magnitude and on the other hand the type dominated by a severe, sometimes necrotic angina, SCHULTZ' "Monocytenangina". Moreover TIDY has pointed out that the disease not infrequently presents only the picture of a long-drawn-out fever without the appearance of either enlarged lymph nodes or angina. He calls this variety the febrile

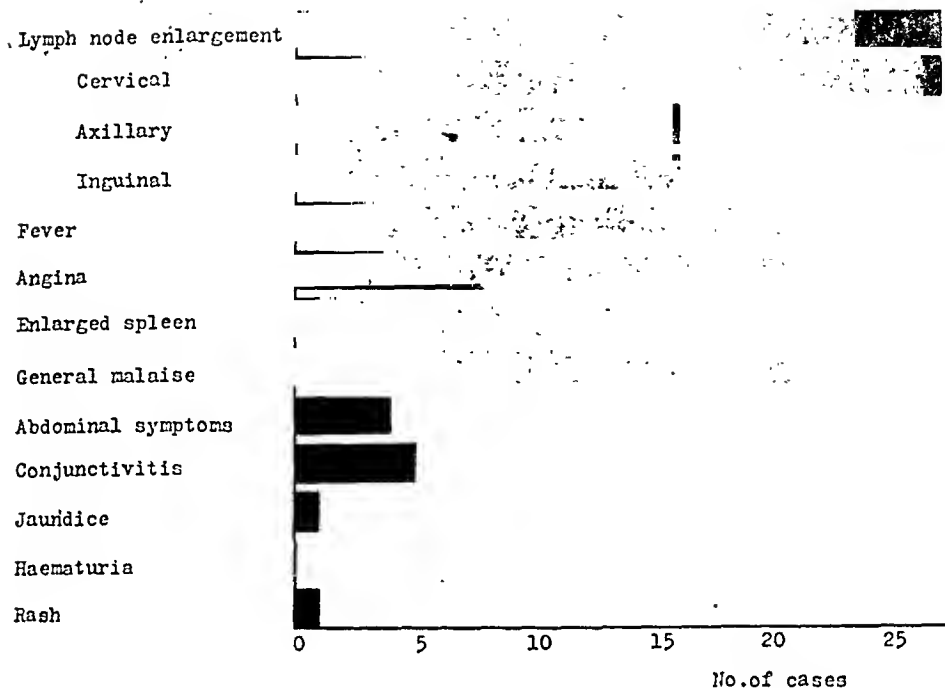


Fig. 2. Outstanding symptoms and physical signs in order of frequency in the author's material, twenty-seven cases (eighteen male, nine female) of infectious mononucleosis.

type. The classification is to a certain extent artificial in that the simultaneous occurrence of intensive angina and large lymph nodes is not rare but it would seem on the whole to correspond to the clinical actualities usually encountered. Less frequent are the cases where the clinical course is given its character according to the presence of, for instance, nephritis, hepatitis, meningo-encephalitis, an exanthema or a probably secondary peritonitis or pneumonia. Common to all cases is the mononuclear blood picture with relative lymphocytosis and the occurrence of characteristic pathological lymphocytes, a peculiar large-celled pleomorphic hyperplasia in the microscopic picture in the enlarged lymph nodes and in the majority of cases the development in the blood of immune substances hemolytic and agglutinating towards sheep red blood cells.

In Figure 1 above, a survey is given of the mutual frequency of the most common clinical symptoms in a series of 50 cases assembled by Mc KINLEY in 1935. For comparison, Figure 2 presents according to similar principles a survey of the writer's material in connection with which the reader is reminded that the latter has

been the object of a certain amount of selection. A survey of the more important clinical data in the present material is presented in Table 1. The details of the cases are submitted in the case histories on page 74.

Those still more interested in the clinical features of the disease are referred first of all to the monographs on the subject by LEHNDORFF and SCHWARZ, TIDY, GLANZMANN, DOWNEY & Mc KINLEY, DOWNEY & STASNEY and NYFELDT. Scandinavian readers are also referred to the works of NYFELDT, THOMSEN & WIMTRUP, ØLLGAARD, RUDEBECK and WISING.

## 2. Sero-Bacteriological Investigations.

### A. BLOOD CULTURES.

Blood cultures was carried out 30 times on altogether 21 patients still suffering from infectious mononucleosis in its acute febrile stage. In all cases except two (cases 3 and 5) the patient presented on the occasion of the examination a temperature of over  $38,0^{\circ}\text{C}$ . in the majority of instances between  $38,5$  and  $39,5^{\circ}\text{C}$ . (see table 1). Scrupulous attention was given to the observation of all possible aseptic precautions.

Twenty-five to thirty cubic-centimeters of blood were aspirated from the cubital vein using heparin or citrate as a noncoagulant and the material was at once inoculated into the different media. Ordinary pepton bouillon Ph 7,3—7,4 and the same with 1 % glucose were mixed with about 5 and 15 % blood respectively. Agar plates were made with portions of the two latter. In cases 6, 8, 9, 12, 13, 18—27 (= twenty-two blood cultures) liver bouillon was also mixed with 5—10 % blood. In all cases tubes of blood also were incubated without any other addition than the citrate or heparin (citrate in cases 1—7, heparin in the others). Incubation was done at  $37^{\circ}\text{C}$ , aerobically and anaerobically. The aerobic incubation took place in ZEISSLER flask, in cases 1—7 with cases 1—7 with water suction, in the other cases in nitrogen with 5 %  $\text{CO}_2$ . In cases 22—27 anaerobic cultivation was also done on pyrogallol plates according to KOCK. After regular inspections of the media the final reading of the results was made after 4 to

	(39.0° C)		significant angina. Spleen not palpable.
14	14	16	Acute onset with fever, general malaise, palpebral edema, and a sore throat. On admission temperature 37.9° C, severe angina, palpebral edema and general enlargement of the lymph nodes. Spleen not palpable.
14	(38.8° C)	(37.7° C)	
	16		
	(37.7° C)		



5 weeks. Specimens from fluid media were then centrifuged and the sediment was examined by direct microscopy in cases 6, 8, 9, 12, 13 and in 18—27 the sediment was also planted on liver bouillon. In the latter way the results were also read off in regard to the specimens which had been incubated without any other addition than heparin or citrate. Aside from the occurrence of staphylococcus albus and diptheroids 4 or 5 times in isolated media, *all substrata in all cases were still sterile after 4 to 5 weeks.*

## B. CULTIVATION EXPERIMENTS WITH LYMPH NODE MATERIAL.

Lymph nodes were extirpated in 16 cases. In one of these it was an enlarged inguinal lymph node (case 21) but in all the others there were from the cervical region. (Cases 1—7, 12—18, 30—24, 26 and 27). All the lymph nodes were extirpated during the initial still febrile stage of the disease (See table 1). All the lymph nodes were removed under strictly aseptic conditions and deprived of their fat. After a small portion had been excised for the microscopic examination, the rest was immediately ground up in a sterile mortar with four parts of sterile saline and filtered through sterile gauze. The resulting suspensions were used for cultivation and inoculation experiments, and in some cases after heating, as antigen for cutaneous and intravenous tests.

In all sixteen cases, immediately after the preparation of the lymph node suspension, it was inoculated into the following media: Ordinary peptone broth of pH 7.3, 1 % glucose broth, the same with 5, 10 and 20 % ascitic fluid, 5 % horse-blood broth, liver broth,<sup>1</sup> serum blood agar, ascites blood agar, horse blood agar, and finally Hohn's egg substratum. Incubation was carried out at 37° under aerobic and anaerobic conditions (ZEISSLER, nitrogen with 5 % CO<sub>2</sub>, Cases 1—7 with only water-suction evacuation.

The cultures were inspected at regular intervals. Final examination was made after 4 to 5 weeks.

Except for the sparse growth of *B. FRIEDLÄNDER* in one case (No. 13), and for the sparse and occasional occurrence (3 or 4 times) of staphylococci and pseudo-diptheria bacilli in single substrates, *all cultures were still sterile after 4 to 5 weeks.*

<sup>1</sup> With the exception of cases 1—7.

## C. EXPERIMENTS WITH STRAINS OF B. NYFELDT.

a) *Bacteriological control.*

It was mentioned in the introduction that NYFELDT assumed that an organism which he called "Bacterium monocytogenes hominis", afterwards classified as belonging to the *Listerella* family (Lister Institute Type Culture 5105), was the cause of infectious mononucleosis in man. NYFELDT recovered this organism in cultures obtained from the blood or cerebrospinal fluid in 8 cases of the disease. The additional support for his claim is his report that in two cases the serum from the patient agglutinated the bacteria found, in the one instance in the dilution 1:250, in the other 1:3200.

In an attempt to illuminate further the possible pathogenetic connection between the NYFELDT bacterium and infectious mononucleosis in man, a number of experiments have been performed with two strains generously placed at the disposal of the writer by Doctor NYFELDT. Both of these strains, designated by NYFELDT as "28" and "37", respectively, had been cultivated from clinically typical cases of infectious mononucleosis.

Control examination of the bacteriological properties of the two strains revealed the characters described by NYFELDT. The organism was a Gram-positive rod, 1—3  $\mu$  in length and about 0.5  $\mu$  in diameter. It grew aerobically, multiplying poorly in ordinary bouillon at pH 7.3 but producing dense cloudiness in liver bouillon in 18 to 24 hours. The results obtained in fermentation experiments are shown in Table 2. On no medium was there gas formation. Only doubtful growth was obtained on dulcitol substratum and the results have therefore been indicated with a question mark in the table. Inconstant results were obtained on a number of other media and these results have been noted with an S? Unquestionable fermentation was obtained on dextrose, saccharose, laevulose, rhamnose, salicin, dextrin and glycerol-fuchsin.

Similar results were obtained by SEASTONE and JULIANELLE among others, in fermentation experiments with a number of *Listerella* strains of human origin as well as from animal sources. The peculiar type of growth in semisolid media, observed by SEASTONE to be common to his *Listerella* strains, was also present in the case of the two strains "28" and "37" furnished by NYFELDT.

TABLE 2.

*Fermentation experiments with the Nyfeldt strains "28" and "37"*

	Nyfeldt "28"		Nyfeldt "37"	
	48 hours	10 days	48 hours	10 days
Dextrose .....	s	s	s	s
Maltose .....	s?	s?	s?	s?
Arabinose .....	O	O	O	O
Dulcitol .....	?	?	?	?
Inocitol .....	O	O	O	O
Rhamnose .....	s	s	s	s
Xylose .....	s?	s?	s?	s?
d-Tartrate .....	?	?	s?	s?
Dextrin .....	s	s	s	s
Salicin .....	s	s	s	s
Glycerol-fuchsin .....	s	s	s	s
Lactose .....	s	s	?	s
Sucrose .....	s	s	s	s
Starch .....	O	s?	O	s?
Sorbitol .....	s?	s?	s?	s?
Laevulose .....	s	s	s	s
Mannitol .....	O	O	O	O

Thus bacteriological control tests would not seem to contradict the assumption that the NYFELDT strains belong to the *Listerella* family.

*b) Inoculation of the Nyfeldt strains into rabbits.*

Two series of experiments were carried out. In the first series two rabbits were injected with strain "28" and two with strain "37". Each animal received intravenously 1 cm<sup>3</sup> of a physiological saline suspension of about 100 million bacteria obtained from an agar culture incubated for 14 days at 37° C. The result may be read off in Table 3 (Rabbits 1—4). The four rabbits developed perhaps a slight leucocytosis but there was no change in proportion between the polymorphonuclear and mononuclear cells in the blood. Neither could any lymph node enlargement be observed either clinically or at autopsy.



TABLE 3.

*Intravenous Inoculation of Rabbits with Nyfeldt's Listerella Strains*

Date	Total leuco-cytes per mm <sup>3</sup>	Poly-morpho-nuc-lears %	Mono-nuc-lears %	Total leuco-cytes per mm <sup>3</sup>	Poly-morpho-nuc-lears %	Mono-nuc-lears %
<i>Rabbit No. 1.</i>				<i>Rabbit No. 2.</i>		
22/2	5400	21	79	5000	14	86
24/2	8300	26	74	9100	18	82
26/2	11300	37	63	10300	32	68
27/2	1 cm <sup>3</sup> "28" (100 million per cm <sup>3</sup> )					
28/2	4900	24	76	9100	20	80
3/3	8000	24	76	12100	18	78
5/3	8600	17	83	9100	13	87
9/3	6800	24	76	9600	27	73
11/3	15000	24	76	11700	20	80
15/3	11300	21	79	9400	17	83
19/3	12100	23	77	10300	20	80
24/3	9400	25	75	9000	21	79
29/3	8500	30	70	9600	15	85
13/4	7800	21	79	9900	29	71
<i>Rabbit No. 3.</i>				<i>Rabbit No. 4.</i>		
22/2	4000	46	54	5700	35	65
24/2	4900	28	72	4900	25	75
26/2	5200	26	74	8000	23	77
27/2	1 cm <sup>3</sup> "37" (100 million per cm <sup>3</sup> )					
28/2	3100	20	80	7000	16	84
3/3	13800	20	80	12700	32	68
5/3	12700	38	62	12300	27	73
9/3	13100	27	73	6700	22	78
11/3	6600	30	70	14200	23	77
15/3	Died 13/3			10300	23	77
19/3				12700	21	79
24/3				10800	25	75
29/3				8700	21	79
13/4				9000	22	78

In view of the result of this experiment a second series, this time of seven rabbits, was inoculated intravenously with the same strains. On the advice of NYFELDT a larger dose was used, about 500—10,000 million bacteria, and the suspension was prepared with physiological saline from the sediment of a liver bouillon culture incubated only 18—24 hours at 37° C. The results may be read off in Table 4 (Rabbits 5—11). The findings may be summarized as follows: The fresh cultures of NYFELDT's strains proved pathogenic for the rabbits inoculated with the stated dose. They developed fever and showed marked general toxic effects. After an incubation period of one or a few days there appeared a more or less pronounced leucocytosis. A passing, relative mononucleosis possibly occurred in one case (Rabbit 9). Otherwise no significant change in the mutual relation between the polymorphonuclear and mononuclear cells could be observed. However the frequency of the large lymphocytes and large monocytic cells with peculiar nuclear forms did increase at the expense of the small lymphocytes. The large cells just mentioned had an extremely polymorphous appearance and their classification is therefore necessarily very uncertain. The cells more or less certainly definable as monocytes have therefore been grouped together under the heading "monocytoid" (Table 4). The variations from day to day in the percentual composition of the blood in regard to the different categories of white blood cells were remarkably great, not infrequently over 100 %, despite careful technique and the taking of the specimens at the same hour each day. Neither clinically nor at autopsy did any of Rabbits 5 to 11 show any lymph node enlargement. Nor could any macroscopic lesions be detected in any of the internal organs at autopsy. Rabbits 5, 6, 7 and 9 died spontaneously with the picture of an acute toxemia. In the three first cases typical rods of the NYFELDT type were recovered on cultivation of blood taken under aseptic precautions by cardiac puncture in connection with the autopsy.



Date	Total leuco- cytes per mm <sup>3</sup>	Neutro- phils  %	Eosino- phils  %	Baso- phils  %	Mono- cytoids and un- certain forms  %	Lymphocytes		Rectal tempe- rature
						Large  %	Small  %	
Rabbit No. 10.								
3/2	7100	27	0.5	0	3	3.5	66.0	38.6
4/2	6500	8	0	3	2	6	81	—
7/2	5300	34	0	0	1	5	60	38.8
7/2 1.0 cm <sup>3</sup> "37" (1000 million per cm <sup>3</sup> )								
9/2	7500	14	0	1	5	11	69	40.2
13/2	14900	19	1	1	4	16	59	38.6
15/2	15700	32	4	1	2	5	56	39.4
17/2	14200	39	2	5	3	9	42	39.2
18/2	11200	39	1	0	6	8	46	38.8
20/2	16400	37	0	1	4	10	48	38.7
22/2	12400	75	0	0	3	5	17	39.0
24/2	13100	61	1	3	3	10	22	—
27/2	8500	37	1	2	2	10	48	—
Rabbit No. 11.								
20/1	5200	12	—	—	6	10	72	—
23/1	5900	6	—	—	6	7	81	—
26/1	6100	8	—	—	4	8	80	—
26/1 1 cm <sup>3</sup> "37" (5000 million per cm <sup>3</sup> )								
28/1	—	13.5	3	—	—	16.5	67	—
30/1	9000	6.5	8.5	—	2	31.5	51.5	38.7
3/2	8300	11	2.5	—	1	36.5	49	39.4
4/2	9800	21.5	1	—	1	18.5	58	—
7/2	9100	5.5	6	—	—	9	79.5	39.1
9/2	9800	13	1.5	0.5	0.5	3	81.5	38.8
13/2	9600	16	1	—	1	4	78	39.6
15/2	10100	14	3	—	3	8	72	—
17/2 0.2 cm <sup>3</sup> "28" (10,000 million per cm <sup>3</sup> )								
18/2	10700	25.5	—	—	3.5	6	65	40.3
22/2	11400	29	11.5	—	8	23.5	28	39.6
24/2	11800	29	5	—	3.5	20.5	42	39.3
27/2	6600	33.5	—	—	8	6	52.5	—

Four more rabbits were inoculated as controls. Two received 2 cm<sup>3</sup> India ink intravenously and the other two 2 cm<sup>3</sup> of a suspension of about 10,000 million bacteria per cm<sup>3</sup> of a staphylococcus albus cultured from the air. All these rabbits developed an exceedingly transient increase in the polymorphonuclear cells with a slight shift to the left but no increase whatever in the number of large lymphocytes or monocytoïd elements. The animals showed no fever and their general condition was unaffected.

Thus on intravenous injection into rabbits the NYFELDT strains "28" and "37" produced an increase in the number of large lympho-



TABLE 5.

Date	Total number of leucocytes	Neutrophils	Eosinophils	Basophils	Lymphocytes	Mono-cytes
23/1/39	14 200	45	2.0	0	49.5	3.5
2/2	Inoculation					
3/2	16 400	79.5	0.5	0	19	1.0
4/2	22 900	79.5	0.5	0	21.5	2.5
6/2	14 400	71.5	1.0	0	24.5	3.0
8/2	16 200	68.5	1.5	0	26	4.0
9/2	15 000	80	0.5	0	16	3.5
10/2	—	80	0.5	0	16	3.5

sized necrotic foci of similar appearance. The spleen was perhaps somewhat larger than normal. The appearance of its cut surface was that seen in an acute infection, somewhat less firm and more like plum-butter than usual. In the inguinal regions and axillae there were a couple of lymph nodes scarcely the size of rice kernels. Otherwise there were no lymph node enlargements in the axillae, inguinal, cervical, praesacral or mesenteric regions. Microscopic examination of the inguinal lymph node revealed normal lymphatic tissue. Figure 3 below shows the microscopic picture of the abscess-like necrotic foci in the omentum and cerebral cortex. Cultivation of blood removed aseptically from the heart lead to the recovery in pure culture of typical *B. NYFELDT*. The hetero-agglutinin titer on the same blood was 1:64 (actual dilution) when carried out according to BUNNEL & PAUL.

*Experiment 2.* *Macacus rhesus* 86 was inoculated 13/2 39 with a suspension (about 2,000 million per cm<sup>3</sup> of the *NYFELDT* strain "37". The suspension was a physiological saline solution of the sediment from a liver bouillon culture incubated for 24 hours at 37° C. The inoculation dose was 0.4 cm<sup>3</sup> intracerebrally and 2.0 cm<sup>3</sup> intraperitoneally. On inspection 24 hours after the inoculation the monkey showed a considerably impaired general condition. On the fourth day there was definite stiffness of the neck which increased markedly the following day. The general condition became very bad with collapse temperature. The impairment progressed until death took place on the sixth evening in a position of opisthotonus.

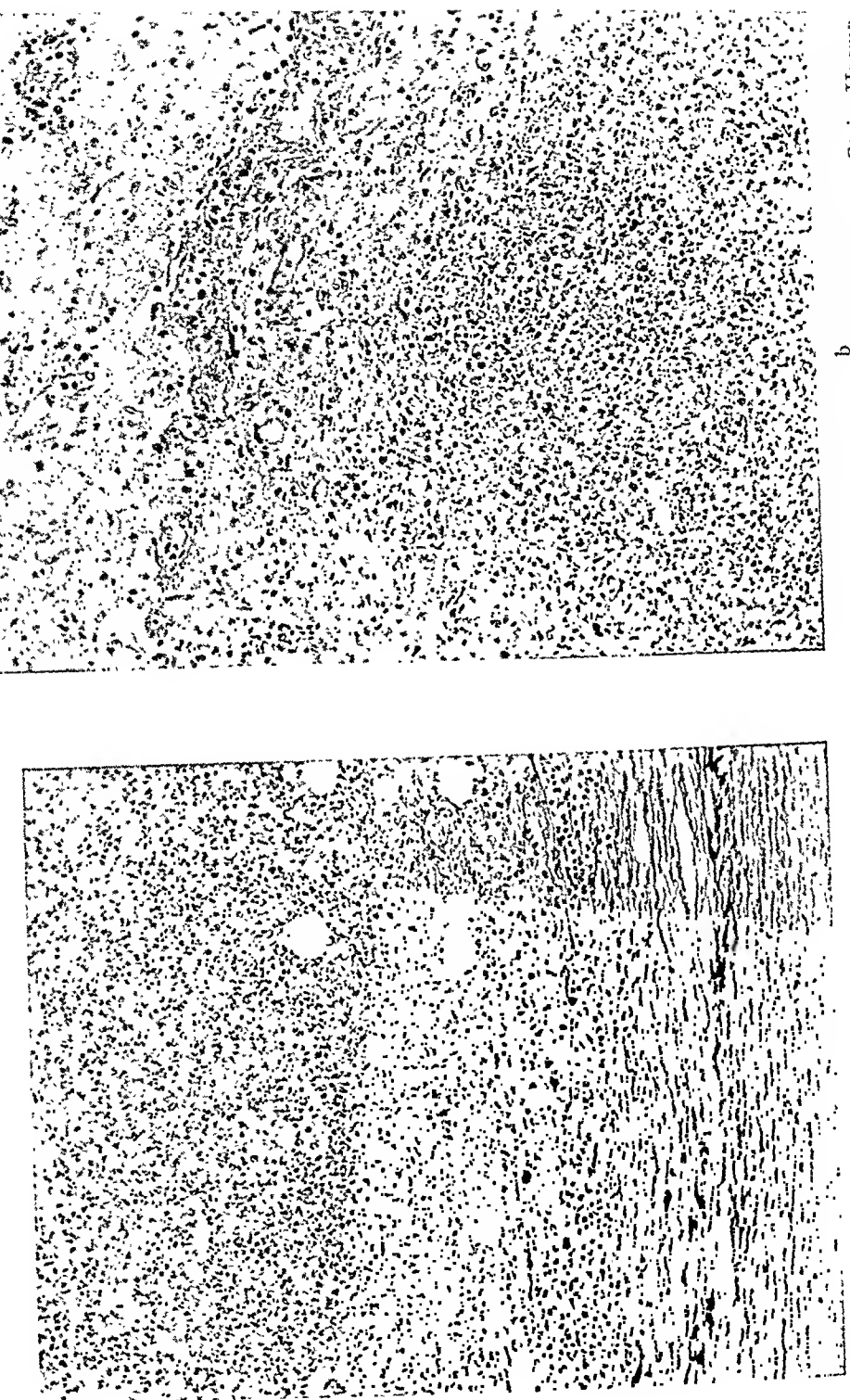


Figure 3. Monkey 85. Abscess-like necrotic foci (a) in the greater omentum and (b) in the cerebral cortex. Stain Haematoxylin-eosin. Photomicrographs  $\times 140$ .

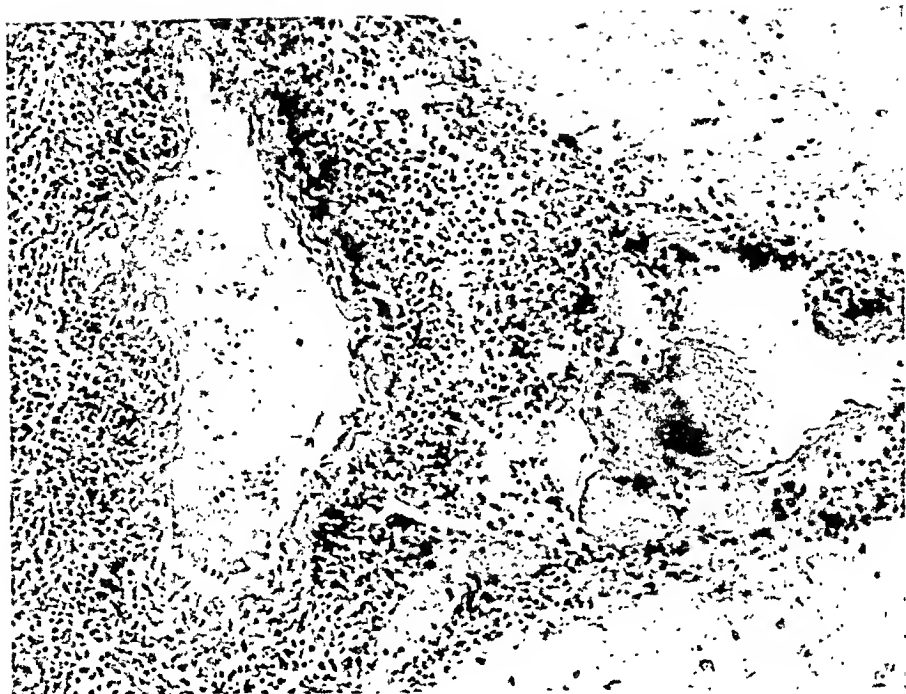


Figure 4. Monkey 86. Massive infiltration of the meninges. Stain haematoxylin-eosin. Photomicrograph  $\times 140$ .

The blood picture during the experimental period showed moderate leucocytosis with a shift to the left. There was a relative lymphopenia without the occurrence of pathological lymphocytes.

Autopsy on Monkey 86 on 20/2 revealed the following: The animal was in rigor mortis in the opisthotonus position. The organs of the thorax and abdomen showed no macroscopic abnormality. The size, consistency and cut surface of the liver and spleen were not abnormal. There were no enlarged lymph nodes anywhere along the sternocleidomastoids or in the axillae, inguinal, praesacral or mesenteric regions. Removal of the cranium revealed marked injection of the vessels of the dura and of the edematous leptomeninges. The fluid in the basal cisterns appeared slightly cloudy. Microscopic examination of an inguinal lymph node half the size of a rice kernel showed no abnormality, the spleen was typical of an acute infection, and the cerebrum and meninges revealed the picture of an acute encephalomeningitis (Figure 4 above). A pure culture of typical *B. NYFELDT* was obtained from the heart blood taken by aseptic puncture. The hetero-agglutinin titer on the same



blood was 1:16 (actual dilution) when tested according to BUNNELL & PAUL.

Thus Bacterium NYFELDT as represented by the two strains obtained from and numbered by NYFELDT himself revealed itself as highly pathogenic for two *Macacus* monkeys, producing in these animals on intravenous injection a rapidly fatal septic infection with suppurative meningitis and encephalitis. It was not possible to demonstrate any reaction from the lymphatic system in the form of lymph node enlargement, lymphocytosis or the occurrence of pathological lymphocytes or monocytic cell elements in the blood. The disease picture thus observed seems to correspond well with that described by a number of workers such as SEASTONE and JULIANELLE in infections in monkeys and other higher mammals with strains of the genus *Listerella*, as well as with the disease picture which several researchers (Table 16, page 62) describe in cases of apparently undoubted *Listerella* infection in man. It was not possible to demonstrate any significant clinical, haematological or pathological similarities between the disease picture produced in the monkey with the NYFELDT bacteria and infectious mononucleosis in man.

#### d) *Serological experiments.*

In order to discover whether infectious mononucleosis causes the formation of antibodies against B. NYFELDT, parallel to the formation of immune bodies demonstrable by the BUNNELL & PAUL reaction, and whether antisera against NYFELDT's bacteria give hetero-agglutination, the following experiments have been carried out.

*Experiment 1.* Suspensions of strains "28" and "37" respectively, were injected intracutaneously into (a) six recently afebrile, convalescent infectious mononucleosis patients with high hetero-agglutinin titers in the serum and (b) as a control into four healthy medical students. The latter had never suffered from any lymph node disease and on the day of the experiment showed a normal blood picture, a normal sedimentation reaction, a normal hetero-agglutinin titer and a negative WASSERMANN reaction. The suspensions of bacteria were in physiological saline, about 10,000 million bacteria per  $\text{cm}^3$  of sediment from a liver bouillon culture

TABLE 6.

Case No.	Ap- prox- imate day of illness	Mono- nuc- lears %	Hetero- agglutinin titer (Actual dilution)	Antigen	Intracutaneous reaction		
					24 hours	48 hours	72 hours
16	15	78	1:1024	Nyf. 28 Nyf. 37 Ty. Pt A + B* Horse serum	45 × 50 30 × 35 25 × 40 15 × 20	1 × 1 0 0 15 × 20	0 0 0 20 × 25
17	11	62	1:4096	Nyf. 28 Nyf. 37 Ty. Pt A + B Horse serum	50 × 55 25 × 55 30 × 40 0	5 × 5 3 × 4 7 × 5 0	1 × 2 1 × 1 7 × 5 0
14	28	81	1:512	Nyf. 28 Nyf. 37 Ty. Pt A + B Horse serum	20 × 30 20 × 30 20 × 25 0	4 × 4 3 × 4 9 × 9 0	0 1 × 1? 0 0
15	about 25	84	1:2048	Nyf. 28 Nyf. 37 Ty. Pt A + B Horse serum	5 × 6 4 × 4 10 × 7 5 × 4	3 × 2 0 7 × 7 1 × 1	0 0 7 × 7 0
18	about 20	87	1:2048	Nyf. 28 Nyf. 37 Ty. Pt A + B Horse serum	40 × 25 20 × 15 37 × 28 3 × 2	1 × 2 1 × 1 2 × 2 0	0 0 0 0
20	8	64	1:2048	Nyf. 28 Nyf. 37 Ty. Pt A + B Horse serum	5 × 7 10 × 10 50 × 70 1 × 1	0 0 10 × 10 0	0 0 1 × 1 0
Control 1 (P. A-g)	—	34.5	1:16	Nyf. 28 Nyf. 37 Saline, 0.5% phenol	80 × 60 30 × 30 0	1 × 2 1 × 1 0	0 0 0
Control 2 (N. Ö-n)	—	32.0	1:32	Nyf. 28 Nyf. 37 Saline, 0.5% phenol	50 × 30 30 × 20 0	2 × 2 1 × 2 0	0 0 0
Control 3 (G. N-n)	—	30.5	1:16	Nyf. 28 Nyf. 37 Saline, 0.5% phenol	100 × 70 10 × 10 0	3 × 3 0 0	0 0 0
Control 4 (P. B-g)	—	40.5	1:16	Nyf. 28 Nyf. 37 Saline, 0.5% phenol	30 × 70 30 × 40 0	1 × 2 1 × 2 0	0 0 0

\* Typhoid, Paratyphoid A + B vaccine.

of strains "28" and "37" respectively, incubated for 18 to 24 hours. Inactivation was carried out twice for 2 hours at 63° on consecutive days. After testing for sterility 0.5 % carbol was added. As a control simultaneous intracutaneous injections were made with horse serum (+ 0.5 % carbol) as well as with typhoid-paratyphoid antigen. (The State Bacteriological Laboratory's injection material against intestinal typhoid-paratyphoid A and B control No. 8, 2,000 million per cubic centimeter). In all the experiments the quantity used was 0.1 cm<sup>3</sup>. Inspection was done after 24, 48 and 72 hours. The results may be found in Table 6.

Experiment 1. shows that no difference could be demonstrated between infectious mononucleosis convalescents and healthy controls in regard to the reaction of the skin to intradermal application of B. NYFELDT.

*Experiment 2.* Sera from 10 recently afebrile infectious mononucleosis convalescents with negative WASSERMANN reactions and with a hetero-agglutinin titer between 1/512 and 1/4096 (actual dilution) were examined for the presence of agglutinins for B. NYFELDT, strains "28" and "37". The reaction according to MÜLLER-WASSÉN<sup>1</sup> was also tested out on these same sera with 0.2 and

<sup>1</sup> Müller himself showed that his flocculation reaction (M.B.R. II) was practicable not only for the diagnosis of lues but also after the introduction of specific antigen such as "Gono-Ballung". Since then Erik Wassén has demonstrated that M.B.R. II can be used generally in serum diagnosis by replacing the NEISSER antigen with some other bacterial antigen in the Gono-Ballung procedure. Wassén proved among other things the extraordinary specificity and value of a "Bang-Ballung Reaction" carried out in this way.

In the writer's experiments the rules of procedure of Müller and Wassén have been carefully observed. The technique has been as follows:

A. *Reagents.*

- 1) Müller-Ballung Reagent II.
  - 2) Bacterial suspension, 20,000 million per cubiccentimeter prepared from sediment of a liver bouillon culture of the Nyfeldt strains "28" and "37", respectively, incubated for 24 hours. Inactivation at 63° for 2 hours on two successive days. After sterility test, addition of 0.5 % carbol.
  - 3) Stock soda solution, 3 % soda in physiological saline.
  - 4) Fresh soda solution, prepared on each occasion from 1 cm<sup>3</sup> of the stock solution + 99 cm<sup>3</sup> physiological salt solution.
  - 5) Diagnosticum, prepared on each occasion from a mixture of one part bacterial suspension and two parts of the fresh soda solution.
- B. *Preparation of the antigen.* 2 cm<sup>3</sup> of Müller-Ballung Reagent II was introduced into an eprouvette 16 mm in diameter and 90 mm long. Into this was run in with a pipette in about 3 seconds 3 cm<sup>3</sup> diagnosticum along the side of the tube. The tube was then turned up and down several times, the end being held closed with the thumb. The temperature of both solutions was preferably 17° C. After 12 minutes

0.3 cm<sup>3</sup> serum. Also in this connection was tested out simultaneously the eventual presence of agglutinins for *Proteus* x<sup>10</sup> antigen. (State Bacteriological Laboratory). As a control were examined the sera from three healthy medical students who had never suffered from lymph node disease and who presented a normal blood picture, a normal sedimentation reaction and a negative WASSERMANN reaction. The result is to be found in the following Table 7.

Experiment 2 shows that with the agglutination and flocculation reactions it was not possible to demonstrate a greater quantity of antibodies against B. NYFELDT in sera from convalescents from infectious mononucleosis than in healthy controls, despite the intense immune body production demonstrable by the high hetero-agglutinin titers. Agglutinins of *PROTEUS* X 19 could not be demonstrated in the convalescent sera.

*Experiment 3.* Immunization against B. NYFELDT was carried out on four healthy medical students (between the ages of 23 and 25) who had never had any lymph node disease and who presented a normal blood picture and normal sedimentation reaction, a negative WASSERMANN reaction and a hetero-agglutinin titer not exceeding 1:32 (actual dilution) when tested according to BUNNELL & PAUL. These students received 20 intravenous injections of either strain "28" or "37" in increasing doses from 0.1 cm<sup>3</sup> to 3.0 cm<sup>3</sup>. The injections were given twice weekly and a suspension of about 1,000 million bacteria per cubic centimeter was used. The suspension was prepared by shaking up in physiological salt solution the sediment from an 18 to 24-hour liver bouillon culture of the respective strain. Inactivation was carried out at 63° C for two hours on two subsequent days. After testing for sterility, 0.5 % carbol was added. Ten days after the last injection, blood was taken from a vein and the serum tested for the presence of agglutinins for the NYFELDT strains. The flocculation test was carried out according to MÜLLER-WASSÉN and the serum was also

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the mixture was transferred to a flask 50 mm in diameter and mixed rapidly, still at 17° C, with 25 cm<sup>3</sup> of the fresh soda solution. The antigen was then ready.

- C. *Execution of the flocculation reaction.* To 0.20 and 0.30 cm<sup>3</sup> serum inactivated at 56° for 30 minutes was added and mixed 0.5 cm<sup>3</sup> antigen. The mixture was placed in a waterbath at 56° C for 25 minutes. It was thereafter kept at room temperature. Reading was done after 18—20 hours. A typical ball in the clear fluid was designated + + +.

TABLE 7.

*Agglutination and flocculation tests with Nyfeldt's Listerella strains "28" and "37" and infectious mononucleosis sera*

Serum from Case No.	Hetero-agglutinin titer (Bunnell & Paul test) Actual dilution	Agglutination of antigen						Flocculation test (Müller-Wassén)		Agglutination of Proteus XI 9		
		Nyfeldt "28"			Nyfeldt "37"			Nyf. "28"	Nyf. "37"	1/20	1/40	1/80
		1:20	1:40	1:80	1:20	1:40	1:80					
5	1:2048	+	±	o	±	o	o	o	o	+	±	o
6	1:4096	+	o	o	±	o	o	o	o	+	o	o
7	1:2048	±	o	o	±	o	o	o	o	+	±	o
9	1:1024	±	o	o	±	o	o	o	o	o	o	o
11	1:512	±	o	o	±	o	o	o	o	o	o	o
12	1:4096	±	o	o	±	o	o	o	o	o	o	o
13	1:1024	o	o	o	o	o	o	o	o	o	o	o
15	1:2048	(±)	o	o	(±)	o	o	o	o	+	(±)	o
17	1:4096	+	o	o	+	o	o	o	o	±	o	o
20	1:4096	+	o	o	±	o	o	o	o	±	(±)	o
Control 1	1:16 (trace)	+	o	o	+	o	o	o	o	+	o	o
Control 2	1:16 (trace)	o	o	o	o	o	o	o	o	+	o	o
Control 3	1:16 (trace in 1:32)	±	o	o	±	o	o	o	o	o	o	o

tested for sheep erythrocyte agglutinins according to BUNNELL & PAUL. As controls were used the sera from three healthy medical students with normal blood status, normal sedimentation reaction and negative WASSERMANN reaction, none of them having received injections of antigen. The results of Experiment 3 may be seen in Table 8.

TABLE 8.

Case	Im- munized against B. Ny- feldt strain No.	Agglutinin titer for		Flocculation reaction		Hetero-agglutinin titer acc. Bunnell & Paul. Final dilu- tion			
		Nyfeldt 28	Nyfeldt 37	Nyfeldt 28	Nyfeldt 37	1:16	1:32	1:64	1:128
B-g, P.	28	1:5120	1:5120	+++ <sup>1</sup> +++ <sup>2</sup>	+++ +++	+	±	o	o
A-g, P.	37	1:640	>1:10240	+++ +++	+++ +++	±	o	o	o
N-n, K.	28	>1:10240	1:10240	+++ +++	+++ +++	±	o	o	o
Ö-n, N.	37	>1:10240	>1:10240	+++ +++	+++ +++	±	o	o	o
Control 1	—	1:20	1:20	— —	— —	±	o	o	o
Control 2	—	o	o	— —	— —	±	o	o	o
Control 3	—	1:20 (trace)	1:20 (trace)	— —	— —	±	±	o	o

<sup>1</sup> Serum dose 0.2 cm<sup>3</sup>. <sup>2</sup> Serum dose 0.3 cm<sup>3</sup>.

Experiment 3 shows that human antisera with a high titer for B. NYFELDT do not contain hetero-agglutinins in increased amounts when tested according to BUNNELL & PAUL. As the table reveals, both strains are agglutinated by serum obtained by immunization with only one of them.

*Experiment 4.* Eight recently afebrile infectious mononucleosis convalescents received intravenously 0.5—1.0 cm<sup>3</sup> of a suspension of the NYFELDT strain "28" or "37". The suspension contained about 10,000 million bacteria per cm<sup>3</sup> and was prepared with physiological salt solution from the sediment from an 18 to 24-hour liver bouillon culture. Inactivation was carried out for 2 hours at 63° C on two subsequent days. After testing for sterility, 0.5 %

carbol was added. The temperature of the experimental persons was controlled for one-half day before and for 36 to 48 hours after the injection of the antigen. During the day the temperature was measured every other hour and during the night, every second or every third hour. As a control, the same amount of antigen was injected into four persons who had never suffered from any lymph node disease and who at the time of the experiment presented a normal blood picture, a normal sedimentation reaction, a negative WASSERMANN reaction and a negative hetero-agglutinin reaction.

The result of the experiment is to be read off in the following Table 9.

TABLE 9

Case No.	Approximate day of illness	Antigen Nyfeldt No.	Volume injected cm <sup>3</sup>	Results
10	23	37	0.5	After 2 hours the temperature had risen 0.4° and after 2½ hours 0.6° C. From then on a normal temperature the entire period.
11	22	28	0.5	Before injection temperature 37.0° C. After 2 hours 38.9°, after 2½ hours 39.3°, after 3½ hours 39.6°, from then on falling. After 4½ hours 38.5°, after 6½ hours 38.1°, after 9 hours 37.5°, from then on no elevation.
12	17	37	0.1	No change in temperature during the 48-hour period of observation.
14	27	37	1.0	No change in temperature during the 48-hour observation with measurement every third hour.
16	15	37	1.0	After injection the temperature rose immediately reaching a maximum in 4 hours with 0.7° rise. After 10 hours the initial temperature was reached and no rise followed in the next 48 hours.
17	10	28	1.0	Injection followed immediately by chills and fever peak with maximum after 2 hours at 39.4° and return 2 hours later. Thereafter no rise in temperature. Observation period 48 hours.
18	21	37	0.5	Immediate temperature rise with maximum at 39.7° after 4 hours. After 10 hours return to initial temperature which then remained normal. Observation period 60 hours.
20	10	37	0.5	Immediate rise in temperature with a maximum 0.5° above the initial temperature after 3 hours. After 6 hours return to initial temperature. Observation period 55 hours.

The experiments with the healthy controls turned out identically with those in Table 9. In both groups several persons showed an immediate rise in temperature after the injection. This temperature

reaction which was often associated with general malaise and chills was over within 9 to 10 hours and occurred in the controls as well as in the infectious mononucleosis patients. It would seem justifiable to interpret the reaction as toxic. There was in no case a rise in temperature after an incubation period.

Experiment 4 thus shows that no difference in the type of reaction could be shown in infectious mononucleosis convalescents and healthy controls after intravenous injection with B. NYFELDT.

It would thus seem as if the result of the serological experiments could be summarized as follows. Immune bodies toward NYFELDT's *Listerella* strains "28" and "37" could not be demonstrated in patients who had just recovered from infectious mononucleosis in any greater quantity than in healthy controls on cutaneous testing, intravenous injection of antigen, by examination for the occurrence of agglutinins or by the flocculation reaction according to MÜLLER-WASSÉN. Human antisera against the NYFELDT strains with high agglutinin titers and positive flocculation reactions according to MÜLLER-WASSÉN proved with the BUNNELL-PAUL technique not to contain sheep erythrocyte agglutinins in a titer exceeding that in healthy controls.

#### D. ATTEMPTS TO TRANSMIT THE DISEASE.

##### *a) Inoculation experiments with rabbits.*

Blood from 10 patients (Cases 8, 9, 12, 21—27) in the acute febrile stage of infectious mononucleosis was inoculated into 12 rabbits. Five to twenty cubic centimeters of heparinized venous blood, as soon as possible and always within 15 minutes after its removal from the patient, was injected intravenously into a vein of the ear of the experimental animal. In one instance the rabbit received 5 cm<sup>3</sup> intravenously and 5 cm<sup>3</sup> intraperitoneally. The animals which survived the primary interference were thereafter subjected to control examination three times a week for three or four weeks in regard to the total number of leucocytes in the blood, the differential blood count and the rectal temperature.

The result of the experiments may be summarized as follows. Four experimental animals who had received intravenous injections of 15—20 cm<sup>3</sup> of human blood from 3 cases (21, 23, 26) of infec-



tious mononucleosis died within 24 hours of the inoculation and at the subsequent autopsy no macroscopic changes could be observed in any of the organs. Two animals for a few days after the injection showed a slight increase in the total number of white blood cells, in the one instance accompanied by a corresponding rise in the percentage of polymorphonuclears, in the other without any significant change in the percentual relation of the leucocytes in the blood. In the remaining six cases there occurred no significant alteration in the total number of white cells during the period of observation. In no case was it possible to discover any significant increase in the percentage of mononuclears. Despite careful technique rather varying values were often obtained for the differential counts on consecutive occasions. In no case did the experimental animals present any rise in temperature or any other clinical symptom whatsoever during the period of observation. In no instance did autopsy after the conclusion of the experiment reveal any lymph node enlargement or other macroscopic change in the inner organs of the animals. Toxoplasms could not be identified in any case in smears from the internal organs of the rabbits.

#### b) *Inoculation experiments with monkeys.*

Attempts to infect monkeys with material obtained from patients suffering from infectious mononucleosis were carried out in a number of cases.

First of all two *Macacus rhesus* monkeys were inoculated with heparinized blood from patients in the acute febrile stage of infectious mononucleosis. The monkeys received 0.4 cm<sup>3</sup> intracerebrally, 20 cm<sup>3</sup> intraperitoneally and 20 cm<sup>3</sup> subcutaneously in one thigh. The animals were inspected and the blood picture studied at least every other day. During a three-week period of observation however, it was not possible to observe any change in the blood picture nor to demonstrate any palpable lymph node enlargement.

On account of the negative result of these preliminary experiments and although attempts to demonstrate antigen by intradermal application of lymph node suspension in infectious mononucleosis patients had given uncertain and intravenous application negative results (Tables 10 and 11), a number of further experiments were carried out using a suspension of extirpated lymph node tissue as

TABLE 10.

Intradermal tests on infectious mononucleosis convalescent with lymph node suspensions (1 to 5 in sterile saline plus 0.5 % phenol) from cases of the same disease in the acute febrile stage.

Case	Mono-nuclears (highest percentage observed)	Hetero-agglutinin titer (actual dilution)	Approximate day of illness	Volume injected	Material from Case	Intradermal reaction		
						24 hrs	48 hrs	72 hrs
2	74	1:1024	9	0.1	1	4×4	3×3	2×2
			11	0.1	2	4×4	2×2	2×2
			11	0.1	saline	0	0	0
4	73	1:512	25	0.1	4	2×2	2×2	1×2
				0.2	4	5×5	3×3	2×2
				0.1	A.T. <sup>1</sup>	20×20	20×20	15×15
				0.1	human <sup>2</sup> serum	0	0	0
5	87	1:2048	25	0.2	6	10×10	10×10	—
				0.2	human <sup>2</sup> serum	0	0	—
6	76	1:4096	24	0.2	6	0	0	0
				0.2	human <sup>2</sup> serum	0	0	0
7	87	1:2048	12	0.2	6	4×5	3×2	—
				0.2	4	4×3	3×2	—
8	68	1:512	15	0.2	4	0	0	0
				0.2	6	0	0	0
				0.2	human <sup>2</sup> serum	0	0	0
				0.2	human <sup>2</sup> serum	0	0	0
9	80	1:1024	15	0.2	4	0	0	0
				0.2	6	0	0	0
				0.2	human <sup>2</sup> serum	0	0	0
12	86	1:4096	19	0.2	4	0	0	0
				0.2	6	0	0	0
				0.2	human <sup>2</sup> serum	0	0	0

<sup>1</sup> Alt Tuberculin 1:1000.

<sup>2</sup> Sterile human serum in saline, 1:5 plus 0.5 % phenol.

TABLE 11.

Intravenous injection into infectious mononucleosis convalescents of inactivated suspensions (1 to 5 in saline) of lymph nodes removed from patients in the acute stage of the same disease.

Case	Approximate day of illness	Antigen from Case	Antigen cm <sup>3</sup>	Results
6	18	6	0.4	During 48-hour observation no rise in temperature, which was measured every second hour.
7	15	4	0.5	During 36-hour observation no rise in temperature which was measured every second hour.
8	15	4	0.5	During 36-hour observation no rise in temperature which was measured every second hour of the day and every third hour of the night.
9	15	6	0.5	During 36-hour observation no rise in temperature which was measured every second hour of the day and every third of the night.
12	19	6	1.0	During 36-hour observation no rise in temperature which was measured every second hour.

the inoculation material, in the hope that a possible pathogenic agent might perhaps occur in greater concentration in the intensely reacting lymph nodes.

Fresh lymph node suspensions from seven cases of infectious mononucleosis (1—7) were inoculated into monkeys. The enlarged cervical lymph nodes were extirpated under the greatest aseptic precautions from patients in the acute febrile stage of the disease. The extirpated node was immediately ground in a sterile mortar with 4 parts of sterile physiological salt solution and then filtered through sterile gauze. The suspension thus obtained was then injected with as little delay as possible into the monkey in question, usually  $\frac{1}{2}$  to 2 hours after the extirpation but in one instance (Case 2) not until 24 hours later. All suspensions were kept at room temperature until the moment they were to be used for the inoculation. The suspensions of monkey lymph nodes which were tested in a number of passage experiments were prepared and stored in exactly the same way.

Simultaneously with the preparation of the different suspensions, either a smear was made or a bit of lymph node tissue was macerated between two cover slips and studied under the microscope directly. Staining was done with alkaline methylene blue and according to GRAM, NEISSER and ZIEHL-NIELSEN. In no instance were any structures encountered which could be interpreted as microorganisms of bacterial nature. Sterility tests on these lymph node suspensions were in all cases negative.

All these experiments were carried out on *Macacus rhesus*, *Macacus cynomolgus* or on *Cercopithecus calitrix*. All the monkeys received 0.3—0.4 cm<sup>3</sup> intracerebrally and 0.5—3.0 cm<sup>3</sup> intraperitoneally or subcutaneously in one thigh. The animals were examined in regard to the blood picture, the temperature and the presence of enlarged lymph nodes before the inoculation and at frequently repeated intervals afterwards. All examinations of the blood picture in a specific monkey were made by the same individual, either the writer or one of two assistants with experience in haematological technique. An attempt was made to take the blood specimens as far as possible at the same time each morning. In all cases the monkeys were autopsied. At autopsy were taken lymph nodes to make the lymph node suspension and for microscopic study, as well as pieces

The results of these experiments on monkeys may be studied in Table 12 which follows.

TABLE 12.

	Date	Blood counts			Remarks
		Number of white blood cells	Poly-morpho-nuclears %	Mono-nuclears %	
Monkey 1 Cercopith. calitr.	<i>Series 1</i>				
	15/10	14000	38.5	61.5	15/10/37: Injection of 0.35 cm <sup>3</sup> of Case I lymph node suspension intracerebrally and 1.5 cm <sup>3</sup> subcutaneously into right thigh. No palpable lymph nodes in axillae or inguinal regions until 3/11 when nodules the size of rice kernels were felt in each inguinal region. During the following days they grew larger and 10/11 there were 2 lymph nodes in the right and 3 in the left inguinal region, the largest being bean-sized. Each axilla contained 3 or 4 nodes as large as rice kernels. Operation 10/11 with removal of lymph nodes in right inguinal region. No significant rise in temperature during observation period.
	19/10	14600	33	67	
	22/10	14300	50	50	
	25/10	19200	23	77	
	1/11	20700	33	67	
	3/11	19700	30	70	
	6/11	19000	23.5	76.5	
	8/11	19100	32	68	
	10/11	13200	26	74	
	11/11	18700	52.5	47.5	
	15/11	18200	50	50	
Monkey 2 Macac. rhes.	10/11	13000	38.5	58.5	10/11/37: Injection of 0.35 cm <sup>3</sup> and 1.5 cm <sup>3</sup> of Monkey I fresh lymph node suspension in the right thigh. No palpable lymph nodes until 22/11 when some the size of rice kernels developed in each inguinal region. During the following days they grew and 29/11 there were 2 or 3 bean-sized nodes in each inguinal region and some up to half that size in the axillae. Operation 29/11. Slight fever up to 39.5° C from 22–26/11.
	15/11	9600	48	52	
	18/11	9200	32.5	67.5	
	20/11	9500	31	69	
	22/11	9000	18	82	
	23/11	8400	21.5	78.5	
	25/11	9000	12.5	87.5	
	27/11	7800	—	—	
	29/11	9300	32	68	
	30/11	17300	58	52	
Monkey 3 Macac. rhes.	29/11	10300	32.5	67.5	29/11/37: Injection of 0.30 cm <sup>3</sup> of Monkey 2 lymph node suspension intracerebrally and 2.5 cm <sup>3</sup> in the right thigh. Before inoculation the animal had had some lymph nodes half the size of rice kernels in both inguinal regions and the axillae. No change until 6/12 when all the lymph nodes seemed enlarged. Each inguinal region 8/12 contained 3 or 4 bean-sized nodes and each axilla some half as large. Operation 8/12. Slight fever up to 39.3° C from 5–8/12.
	30/11	12000	41.5	58.5	
	2/12	7800	34.5	65.5	
	6/12	6800	18	82	
	7/12	6400	23.5	76.5	
	8/12	4900	21.5	78.5	
	13/12	9900	30	70	
Monkey 4 Macac. rhes.	8/12	18800	51	49	8/12/37: Injection of 0.4 cm <sup>3</sup> of lymph node suspension intracerebrally and 2.0 cm <sup>3</sup> subcutaneously in the right thigh. No palpable lymph nodes until 13/12 when they could be felt enlarged in both axillae and inguinal regions. On 20/12 there were 4 nodes in the right and 3 in the left inguinal region up to the size of beans and peas and some about half that large in the axillae. Operation 2/12. No significant rise in temperature.
	10/12	14500	44	56	
	13/12	7300	32	68	
	15/12	7100	22.5	77.5	
	17/12	8100	24	76	
	18/12	8200	17	83	
	20/12	6400	16	84	
	29/12	8200	29	71	

	Date	Blood counts			Remarks
		Number of white blood cells	Poly-morpho-nuclears %	Mono-nuclears %	
Monkey 5 Macac. cynomolg.	20/12	12900	62	38	20/12/37: Injection of 0.3 cm <sup>3</sup> of Monkey 4 lymph node suspension intracerebrally and 2 cm <sup>3</sup> in the right thigh. No palpable lymph nodes before inoculation but by 4/12 some half the size of rice kernels were felt in both inguinal regions. By 31/12 each inguinal region and each axilla contained nodes up to the size of beans. Operative removal 31/1/38 of 2 bean-sized lymph nodes from the right inguinal region. Slight fever up to 39.1° C from 28–31/12.
	22/12	5900	19	81	
	24/12	9000	16	84	
	27/12	10400	41	59	
	29/12	11200	29	71	
	31/12	9200	52.5	47.5	
Monkey 6 Macac. rhes.	3/1	16000	43	57	3/1/38: Injection of 0.3 cm <sup>3</sup> of Monkey 5 lymph node suspension intracerebrally and 1 cm <sup>3</sup> in the right thigh. Before inoculation some palpable lymph nodes in both axillae and inguinal regions but none larger than rice kernels. During entire observation period to 28/1 no enlargement of nodes detected nor any fever.
	7/1	8000	58.5	41.5	
	10/1	6900	33.5	66.5	
	15/1	7300	31	69	
	18/1	13200	40.5	59.5	
	21/1	12700	37	63	
	25/1	7900	42	58	
	28/1	8700	49.5	50.5	
Monkey 10 Cercopith. calitr.	Series 2				4/4/38: Injection of 0.3 cm <sup>3</sup> of Case 2 lymph node suspension intracerebrally and 0.8 cm <sup>3</sup> in the right thigh. Before inoculation each axilla and inguinal region contained 1 or 2 lymph nodes the size of rice kernels. No definite enlargement until 21/4. Operative removal 26/4 of two bean-sized lymph nodes from the right inguinal region. Slight fever up to 39.2° C from 20–26/4.
	4/4	19100	40.5	59.5	
	5/4	12400	—	—	
	8/4	18500	46	54	
	12/4	12300	39.5	60.5	
	14/4	14800	42	58	
	21/4	16200	37.5	62.5	
	26/4	17600	27	73	
Monkey W 1 Macac. rhes.	6/5	10600	29	71	26/4/38: Injection of 0.3 cm <sup>3</sup> of Monkey W. 1 lymph node suspension intracerebrally and 1.5 cm <sup>3</sup> in the right thigh. No palpable lymph nodes before inoculation but by 5/11 several the size of rice kernels in each inguinal region. These grew until 19/5 when each inguinal region and axilla contained 2 or 3 nodes up to the size of beans. No significant fever. Operation 19/5 and inoculation into a new monkey which however did not develop any symptoms during one month of observation.
	26/4	12200	43	57	
	29/4	14600	47.5	52.5	
	2/5	9800	40	60	
	5/5	10600	26	74	
	11/5	14600	25	75	
	15/5	10200	39.5	60.5	
	19/5	7900	44	66	
Monkey A. L. 40 Macac. cynomolg.	25/5	11000	46	54	12/10/38: Injection of 0.3 cm <sup>3</sup> of Case 4 lymph node suspension intracerebrally and 2.0 cm <sup>3</sup> intraperitoneally. No palpable lymph nodes in axillae or inguinal regions until 19/10 when both inguinal regions contained some of the size of rice kernels. These grew and on 22/10 there was one bean-sized node in the left inguinal region, two half that size on the right and several the size of rice kernels in the left axilla. Autopsy 25/10. Slight fever from 18–25/10.
	Series 3				
	12/10	—	34	66	
	13/10	17800	38.5	61.5	
	Inoculation .....				
	14/10	13600	44	56	
	15/10	12000	43	57	
	17/10	15000	37.5	62.5	
	18/10	13100	41	59	
	19/10	10400	35.5	64.5	
	20/10	10700	33.5	66.5	
	21/10	14400	24.5	75.5	
	22/10	12700	22.5	77.5	
	24/10	15400	30.5	69.5	
	25/10	16500	35.5	64.5	

	Date	Blood counts			Remarks
		Number of white blood cells	Poly-morpho-nuclears %	Mono-nuclears %	
Monkey A. L. 58 Macac. cynomolg.	25/10	17700	37	63	25/10/38: Injection of 0.3 cm <sup>3</sup> of Monkey A. L. 40 lymph node suspension intracerebrally and 1.5 cm <sup>3</sup> intraperitoneally. At inoculation each inguinal region contained a couple of lymph nodes up to the size of rice kernels but the axillae none. On 4/11 all lymph nodes seemed definitely enlarged with some bean-sized in each inguinal region and peasized in each axilla. Autopsy 4/11. No significant rise in temperature.
	Inoculation .....				
	26/10	24400	48.5	51.5	
	27/10	26400	33.5	66.5	
	28/10	17100	29.5	70.5	
	29/10	16300	17.5	82.5	
	31/10	15400	18	82	
	1/11	17000	13	87	
	2/11	16300	—	—	
	3/11	15400	23	77	
Monkey A. L. 37 Macac. rhes.	4/11	17400	30	70	
	3/11	12100	38	62	4/11/38: Injection of 0.3 cm <sup>3</sup> of Monkey A.L. 58 lymph node suspension intracerebrally and 1.5 cm <sup>3</sup> intraperitoneally. No palpable lymph nodes before inoculation or until 10/11. By 15/11 there were three pea-sized nodes in the right and two half as large in the left inguinal region and one the same size in the left axilla. Autopsy 15/12. Fever up to 38.8° C from 9—15/11. On 15/11 lymph node suspension from this Monkey A.L. 37 was inoculated intracerebrally (0.3 cm <sup>3</sup> ) and intraperitoneally (0.3 cm <sup>3</sup> ) into Macacus cynomolgus S.S. 2 which however did not develop symptoms during 24 days of observation.
	4/11	11500	37.5	62.5	
	Inoculation .....				
	5/11	12300	49	51	
	7/11	12800	57.5	42.5	
	8/11	12600	38.5	61.5	
	9/11	12200	22	78	
	10/11	11200	29	71	
	11/11	13100	55.5	44.5	
	12/11	14000	66.5	33.5	
Monkey K. L. 1 Cercopith. calitr.	14/11	12400	67	33	
	15/11	11100	48	52	
	Series 4				4/4/38: Injection of 0.3 cm <sup>3</sup> of Case 3 lymph node suspension intracerebrally and 0.8 cm <sup>3</sup> subcutaneously in the right thigh. Before injection there were a couple of palpable nodes half the size of rice kernels in each inguinal region. On 21/4 definitely enlarged nodes were palpated, one bean-sized in each inguinal region and one half that size in each axilla. Autopsy 26/4. No significant rise in temperature during the time of observation. On 26/4 lymph node suspension from this monkey K.L. 1 was inoculated intracerebrally (0.3 cm <sup>3</sup> ) and intraperitoneally (2.0 cm <sup>3</sup> ) into Monkey W. 2 which however did not develop any symptoms during one month of observation.
	4/4/38	19100	39	60	
	Inoculation .....				
	5/4	12400	23	77	
	8/4	13200	40	60	
	10/4	14000	36	64	
	12/4	18400	53	47	
	14/4	16400	29	71	
	17/4	14700	35	65	
	21/4	10600	26	74	
Monkey 83 Macac. rhes.	24/4	13500	29	71	
	26/4	14300	37	63	
	Series 5				19/12/38: Injection of 0.4 cm <sup>3</sup> of Case 7 lymph node suspension intracerebrally and 3.0 cm <sup>3</sup> intraperitoneally. Before inoculation each inguinal region contained one lymph node the size of a rice kernel. From 27—31/12 there was a slight rise in temperature (about 1° C) and 31/12 it seemed as if the inguinal and axillary glands were enlarged. On 4/1 the inguinal regions contained some nodes up to the size of beans and in the axillae were some nodes as large as peas. Autopsy 12/1. No passage attempted in this case.
	19/12	12200	48.5	51.5	
	Inoculation .....				
	20/12	15600	72.5	17.5	
	21/12	14200	66.5	33.5	
	22/12	11800	39.5	60.5	
	23/12	9000	62	38	
	24/12	15700	44.5	55.5	
	27/12	10800	65.5	34.5	
	28/12	10500	60	40	
	29/12	8000	50.5	49.5	
	30/12	11400	65.5	34.5	
	31/12	10500	66	34	
	2/1 39	11300	52.5	27.5	
	3/1	10800	33	67	
	4/1	10000	57	43	
	7/1	10400	61.5	38.5	
	9/1	10900	74	26	
	10/1	7200	58	42	
	11/1	10300	40.5	39.5	
	12/1	9500	31	69	

	Date	Blood counts			Remarks
		Number of white blood cells	Poly-morpho-nuclears %	Mono-nuclears %	
Monkey 82 Macac. rhes.	Series 6				16/12/38: Injection of 0.4 cm <sup>3</sup> of Case 6 lymph node suspension intracerebrally and 5.0 cm <sup>3</sup> intraperitoneally. Before inoculation and until 28/12 no palpable lymph nodes. On 28/12 nodes the size of rice kernels in each inguinal region and one pea-sized node in the right axilla. The lymph nodes then grew until autopsy 31/12 when one bean-sized node and two up to the size of rice kernels were found in each inguinal region. The axillae contained none but there were two small presacral nodes. Before inoculation the temperature was 38.3° C. On 19/12 it began to rise reaching 39.6° C the next day. On 24/12 it fell but then rose gradually until the day of the autopsy. On 31/12 lymph node suspension from this monkey 82 was inoculated into Macac. rhesus 85 which however did not develop any symptoms during one month of observation.
	16/12/38	26900	50	50	
	Inoculation .....				
	17/12	36900	68.5	31.5	
	19/12	25500	50.5	49.5	
	20/12	27200	61	39	
	21/12	25000	47	53	
	22/12	20500	47.5	52.5	
	23/12	22000	48	52	
	24/12	18900	41.5	58.5	
	27/12	23200	42	58	
	28/12	20900	51.5	48.5	
	29/12	23600	45.5	54.5	
	30/12	24700	45.5	54.5	
	31/12	21600	61	39	
Monkey 81 Macac. rhes.	Series 7				7/2/38: Injection of 0.4 cm <sup>3</sup> of Case 5 lymph node suspension intracerebrally and 4.0 cm <sup>3</sup> intraperitoneally. Before inoculation and until 16/12 no palpable lymph nodes. On 16/12 the axillae each contained a few nodes the size of small rice kernels, and the inguinal regions a few half the size of peas. These then increased in size and on 19/12 those in the axillae were pea-sized and those in the inguinal regions bean-sized. On 16/12 the temperature gradually began to rise after having been around 38° C. On 23/12 the temperature was 39.5° C. Autopsy the same day.
	6/12/38	8700	49.5	50.5	
	7/12	9900	59	41	
	Inoculation .....				
	8/12	11400	44	54	
	9/12	12600	50	50	
	10/12	12600	61	39	
	12/12	11500	70.5	29.5	
	13/12	8800	55	45	
	14/12	12400	47.5	52.5	
	15/12	15600	33.5	66.5	
	16/12	13200	48	52	
	17/12	12100	46.5	53.5	
	19/12	15100	44	56	
	20/12	13100	57	43	
	21/12	13700	55	45	
	22/12	13700	46	54	
	23/12	12300	51	49	
	Monkey 84 Macac. rhes.	23/12	19800	52	
Inoculation .....					
24/12		29500	65	35	
27/12		24000	59.5	40.5	
28/12		17300	52	48	
29/12		12300	51.5	48.5	
30/12		14500	49.5	50.5	
31/12		14500	52	48	
2/1		23100	66.5	33.5	
3/1		18700	42	48	
4/1		18900	60.5	39.5	
7/1		21500	63	37	
9/1		21500	59.5	40.5	
10/1		19800	60	40	
11/1		15800	53	47	
12/1	15000	44.5	55.5		

of the organs for microscopic examination and a specimen of blood for testing the presence of hetero-agglutinins according to Bunnell & Paul. Blood was not taken before the inoculation because it seemed unwise to risk cardiac puncture in view of the difficulty of obtaining experimental animals.

The results of the experiments described in Tabelle 12 above may be summarized as follows.

### *Clinical data.*

*Series 1.* About 18 days after inoculation with lymph node material from Case I, Monkey 1 developed enlarged lymph nodes in the axillae and inguinal regions as well as possibly a slight increase in the relative occurrence of mononuclear cells in the blood. On the 25th day a lymph node suspension was passed to Monkey 2 which after about 14 days developed generalized enlargement of the lymph nodes, a slight rise in temperature and an increase in the number of mononuclears in the blood. On the 19th day a lymphoma suspension from Monkey 2 was inoculated into Monkey 3 which after about 10 days also developed enlarged lymph nodes, a slightly elevated temperature and an increase in the number of mononuclear cells in the blood. Passage from Monkey 3 to Monkey 4 done on the 10th day and from Monkey 4 to Monkey 5 on the 12th day after the inoculation gave identical results after about the same length of time. On the 15th day after inoculation, a lymphoma was extirpated from Monkey 5 and a suspension of it prepared in the usual way was injected into Monkey 6. In the latter animal however during a four-weeks period of observation there was never observed any lymph node enlargement, temperature elevation or alteration in the blood picture.

*Series 2:* About 17 days after inoculation with lymph node material from Case 2, Monkey 10 developed enlarged lymph nodes in the axillae and inguinal regions, a slight elevation in temperature and an uncertain, slight increase in the number of mononuclear cells in the blood. On the 22nd day after the inoculation, passage of lymphoma suspension was carried out to Monkey W. 1 which after about 2 weeks presented enlarged lymph nodes in the axillae and inguinal regions, probably a slight increase in the number of mono-



nuclear cells in the blood but no elevation in temperature. On the 23rd day after the inoculation passage was done from Monkey W. 1 to a new monkey which however during a month of observation presented no evidence of lymph node enlargement, alteration in the blood picture or elevation in temperature.

*Series 3:* About 10—12 days after the inoculation with lymph node material from Case 4, Monkey A. L. 40 developed lymph node enlargements, a slight increase in the number of mononuclear cells in the blood and possibly a slight rise in temperature. On the 14th day passage was done with lymph node suspension from this animal to Monkey A. L. 58 which after 8 to 10 days presented apparently certain lymph node enlargements, an increase in the number of the mononuclear cells in the blood but no elevation in temperature. On passage to Monkey A. L. 37 from Monkey A. L. 58 on the 10th day after inoculation, the former animal developed on the 6th day a rise in temperature and a few days later lymph node enlargement and a transient increase in the number of mononuclear cells in the blood. Passage on the 10th day from Monkey A. L. 37 to a new monkey gave negative results. During an observation period of 24 days there was no change in the lymph node status, the blood picture or the temperature.

*Series 4:* About 10—15 days after the inoculation of lymph node material from Case 3, Monkey K. L. I developed enlarged lymph nodes which persisted until the passage experiment on the 22nd day. No change in the blood picture or temperature could be observed in this monkey. On the 22nd day, passage with lymphoma suspension to another monkey gave negative results. During one month of observation the latter monkey showed no lymph node enlargement, no change in the blood picture nor any elevation in temperature.

*Series 5:* About 12 to 15 days after inoculation with lymph node material from Case 7, Monkey 83 developed possibly slight enlargement of lymph nodes in the axillæ and inguinal regions, perhaps a slight elevation in temperature but no change in the blood picture. Further passage was not attempted in this case.

*Series 6:* About 13 days after inoculation with lymph node material from Case 6, Monkey 82 presented slight general lymph node enlargement and soon after a slight rise in temperature. No change in the blood picture could be observed. Passage was carried out on

the 16th day to Monkey 85 which during one month of observation did not show lymph node enlargements, changes in the blood picture or an elevation in temperature.

*Series 7:* About 9 days after inoculation with lymph node material from Case 5, Monkey 81 showed slight but apparently certain lymph node enlargement which increased during the following days. At the same time there was a slight elevation of the temperature but no change in the blood picture. On the 18th day passage was done to Monkey 84 which after 9 or 10 days seemed to have definitely enlarged inguinal and axillary lymph nodes and possibly a slight elevation in temperature but no change whatsoever in the blood picture. Further passage was not undertaken.

Serum for the Bunnell & Paul reaction was obtained at autopsy on seven of the monkeys. The following sheep erythrocyte titers were then obtained: Monkey A. L. 40 1/16, A. L. 58 1/32, A. L. 37 1/32, No. 81 1/128, No. 84 1/64, No. 82 1/128, No. 83 1/128. As a control the serum was examined from 8 monkeys who had been sacrificed after they had given negative results to injections of water suspected of containing poliomyelitis virus. These controls gave the following hetero-agglutinin titers: 0, 0, 0, 0, 1/16, 1/64, 0, 0.

#### *Pathological data and microscopy.*

At autopsy on the inoculated monkeys the internal organs showed in no case any clearly observable gross lesions. In no case were the liver or spleen definitely enlarged. The consistency and cut surface were normal although in one case the cut surface of the spleen could possibly be described as somewhat more spongy than usual. In no case were abscesses or other evidence of septicemic infection encountered as after inoculation with B. NYFELDT. The picture of a pseudotuberculosis such as that described by BLAND in connection with inoculation with *Toxoplasma cuniculi* was not observed in any case. The only macroscopic changes were the lymph node enlargements in the axillæ and inguinal regions and in a few cases (Monkeys 1, 2, A. L. 58) in the praesacral region. The bronchial and mesenteric lymph nodes seemed in all cases to be of normal size. The lymph nodes along the sternocleidomastoid were seldom as obviously enlarged as those in the inguinal regions and axillæ.

The brain as well as the axillary or inguinal lymph nodes or both were preserved in every case.

The preserved brains showed neither gross nor microscopic evidence of meningitis or encephalitis. Microscopic examination was done on the brains from Monkeys A. L. 58, A. L. 37 and numbers 81, 82, 83 and 84.

The preserved lymph nodes all presented macroscopically a light grayish-red, bulging cut surface of about the same appearance as in man. The lymph nodes were soft, without periaidenitic adhesions and up to the size of brown beans.

Microscopic examination of sections from these formalin-fixed lymph nodes (1) stained by the usual methods and (2) unstained and photographed in ultraviolet light at the nuclei acid absorption maximum (2570 Å) revealed the following.

Sections of lymph nodes from Monkeys 1—5 (Series 1) all showed a microscopic picture closely similar to that in human lymph nodes in infectious mononucleosis. There was the same peculiar diffuse pleomorphic large-celled hyperplasia with more or less disappearance of follicles. Most pronounced were the changes in sections from Monkeys 2 and 3 (Figures 5 and 6). These alterations were least distinct in sections from Monkey 5. Sections from lymph nodes from Monkey W. 1 (Series 2, Figure 7) and from Monkey A. L. 40, 58 and 37 (Series 3) also all showed the same microscopic picture with more or less obliteration of the lymph node structure and large-celled hyperplasia with mononuclear cells present in profusion (Figures 7 and 8). In the sections from Monkey A. L. 37 the changes were less pronounced than in those from Monkey A. L. 40 and 58. Perilymphadenitis was not observed.

Sections of lymph nodes from the monkeys which after inoculation of lymph node material did not show any clinical changes in the blood but nevertheless did develop enlarged lymph nodes sometimes presented a picture similar to that described in the preceding paragraph although the changes in these cases were considerably less pronounced. The alterations in these cases could best be described as a slight general hyperplasia, occasionally with isolated foci of a large type of cell. The picture however was not polymorphous in the same way and the general lymph node architecture was retained in all of these cases. Mononuclear cells occurred rather

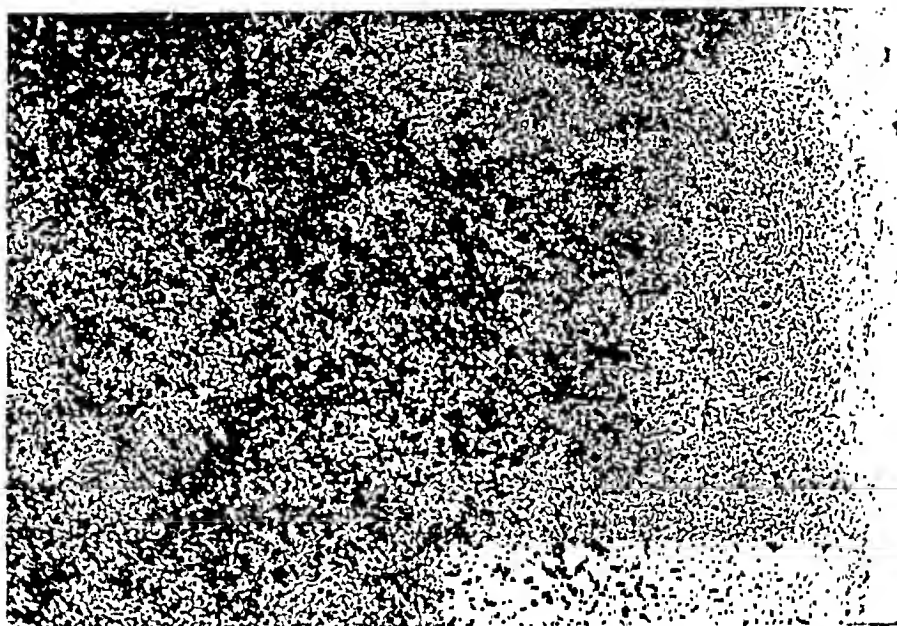


Fig. 5. Section from inguinal lymph node of Monkey 2 after inoculation with lymph node suspension from Monkey 1 which had been injected with lymph node suspension from an infectious mononucleosis patient. Compare Fig. 1,4 a. Haematoxylin-eosin. Photomicrograph  $\times 60$ .

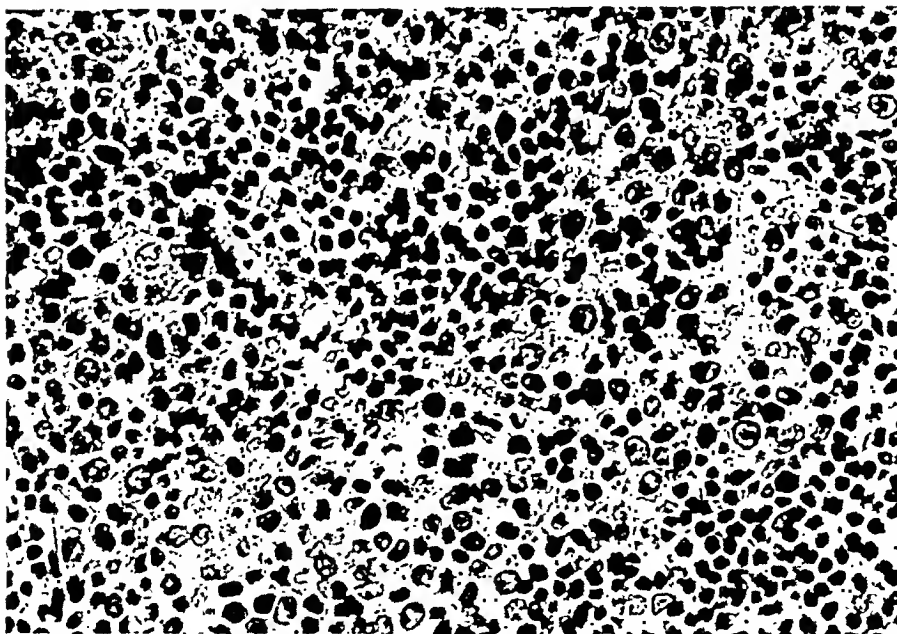


Fig. 6. Section from inguinal lymph node of Monkey 3. Compare Fig. 1,4 b. Haematoxylin-eosin. Photomicrograph  $\times 400$ .

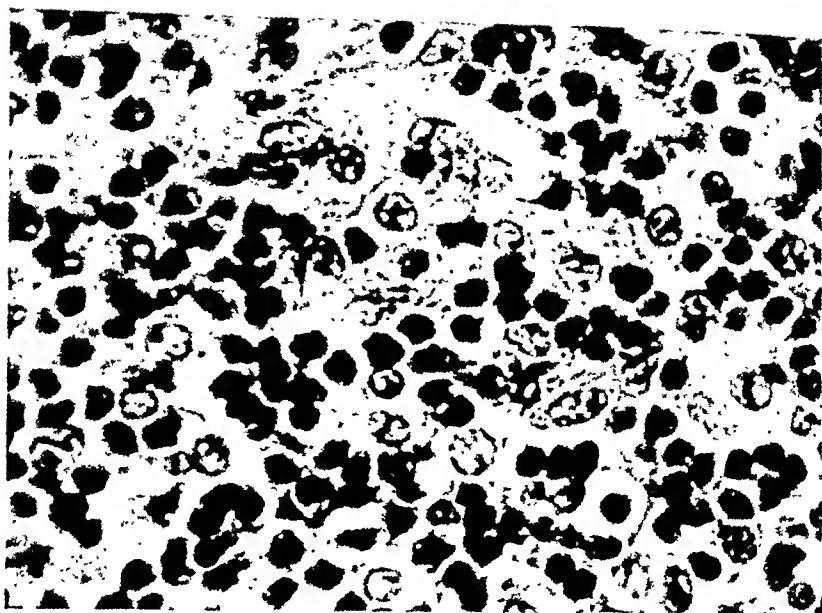


Fig. 7. Section from inguinal lymph node of Monkey W 1 after inoculation with lymph node suspension from Monkey 10 which had been injected with lymph node suspension from an infectious mononucleosis patient. Haematoxylin-eosin. Photomicrograph  $\times 1000$ .

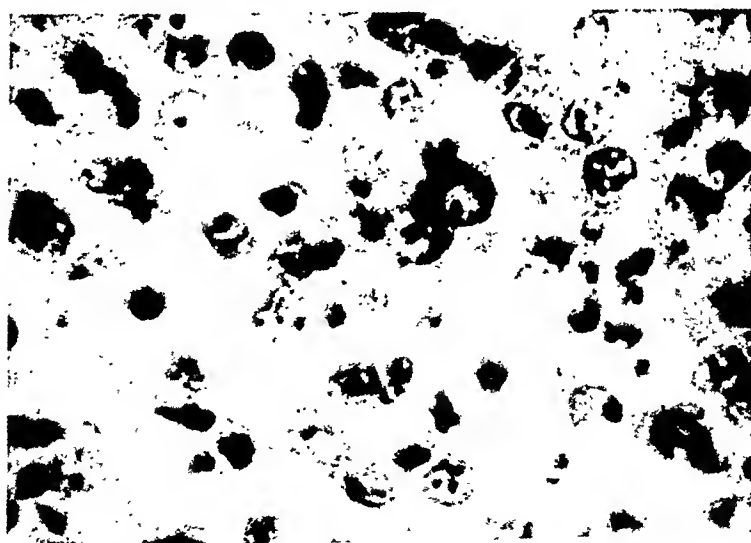


Fig. 8. Section from inguinal lymph node of Monkey A. L. 58 after inoculation with lymph node suspension from Monkey A. L. 40 which had been injected with lymph node suspension from an infectious mononucleosis patient. Formol-fixed unstained section. Photomicrograph at 2570 Å,  $\times 1190$ .

profusely in a number of sections of Monkeys 81 och 82, in the latter of which plasma cells were prominent.

In no case were there encountered in the sections any structures which could be interpreted as microorganisms of bacterial nature. Aerobic and anaerobic cultures from suspensions of extirpated lymphomas on current substrates (ordinary bouillon of pH 7.3, glucose, ascites and liver bouillon, ascites and blood agar plates) all gave negative results.

Sections from lymph nodes from six healthy monkeys which were examined as controls showed only the picture of normal lymphatic tissue with well retained structure and nowhere the large-celled polymorphous hyperplasia described above.

### *c) Attempts to transmit the disease to man.*

The experiments on rabbits and monkeys described in the preceding seem to show that neither of these animals is suited for testing out the possible pathogenic agent of infectious mononucleosis. The rabbit appears unsuitable not merely in view of the negative results of the inoculation experiments but also because this animal seems to present such a pronouncedly labile blood picture and a normal mononuclear differential count which apparently can be accentuated by different causes. It would appear as if the results of the experiments with *Macacus* and *Cercopithecus* monkeys are not sufficiently constant even if they were conceded to be probably successful transmissions of the disease and therefore these animals cannot be regarded as sufficiently susceptible to the malady that they can be recommended as experimental subjects. In consideration of the above, experimental attempts to transfer infectious mononucleosis to man seemed desirable, as well as warranted, in view of the benign character of the disease.

As experimental subjects were chosen medical students who volunteered for the purpose. The requirements drawn up in regard to the health of these volunteers were as follows: Only those were accepted who had previously been in excellent health, who on the occasion of the examination presented no lymph node enlargements or other disease symptoms, who had a normal blood status, a normal sedimentation reaction, negative WASSERMANN and negative

TABLE 13

Case Age and Bunnell & Paul test	Inoculation method and quantity	Results
F—n, N. O. 24 years B-P (1:16)	2 cm <sup>3</sup> suspension of Case 4 subcutaneously into left thigh. In addition the tonsils were painted with suspension.	Neither locally, regionally nor elsewhere did the lymph nodes show any reaction during the observation period. The blood picture also remained completely unaltered the whole time. There was no rise in temperature.
H—l, G. 26 years B-P (1:16)	4.0 cm <sup>3</sup> suspension of Case 6 subcutaneously in left supra-clavicular fossa plus painting of tonsils.	There were no clinical symptoms whatever or any change in the blood picture during 4 weeks of observation.
V—s, S. 21 years B-P (1:16)	4.0 cm <sup>3</sup> suspension of Case 4 subcutaneously in left supra-clavicular fossa plus painting of tonsils.	The day after inoculation there was a slight increase in the total number of white blood cells (from 5,000 to 10,900) with an increase in the polymorphonuclears. Three days later the blood picture was the same as before. There was no increase in the number of lymphocytes during the observation period. The temperature remained normal and there was no enlargement of lymph nodes.
F—k, A. 24 years B-P (1:16)	After being stored frozen for 15 days the suspension from Case 4 was melted and 1 cm <sup>3</sup> injected subcutaneously into the left thigh anteriorly just below the inguinal ligament. In addition the tonsils were rubbed with the suspension and drops of it were inserted in each nostril.	During the period of observation there were no symptoms whatever either locally or in the form of enlarged lymph nodes or fever. The blood picture remained unaltered the whole time.
H—t, O. 24 years B-P (1:64)	2.0 cm <sup>3</sup> suspension of Case 3 injected subcutaneously into left thigh. In addition 0.5 cm <sup>3</sup> was inserted in the nostril.	Small lymph nodes the size of rice kernels palpable in both inguinal regions before the inoculation seemed after a few days to be somewhat larger. On the 9th day there was one lymph node in the left inguinal region half the size of a brown bean. The blood picture the first 10 days showed a slight increase in white cells (from 6—7,000 to 10—11,000) with possibly a certain increase in the mononuclears (from 26% to 43% in the 9th day with a decrease from then on). There was no rise in temperature and there were no other enlarged nodes.
B—m, I.-L. 26 years B-P (0 agglut.)	Suspension from Case 24 was diluted 1:10 with physiological saline and filtered through Chamberlain L 3. 2 cm <sup>3</sup> were injected intravenously, 2 cm <sup>3</sup> subcutaneously in one tonsil and about 1 cm <sup>3</sup> was sprayed into the nose.	There were no clinical symptoms whatever or any changes in the blood picture during the month of observation.

flocculation reactions and a hetero-agglutinin titer less than 1:64 (actual dilution), according to BUNNELL & PAUL.

Six such volunteers were inoculated with freshly prepared lymph node suspension from four cases of infectious mononucleosis. The suspension had been made up as described on page 40 and sterility tests on common substrates were in all cases negative. After the inoculation the volunteers were carefully followed for three or four weeks in clinical respects as well as in regard to the blood picture. Table 13 summarizes the six experiments.

As Table 13 shows, no clinical or significant haematological changes arose in any of these 6 cases in connection with the inoculation.

In two cases volunteers were inoculated intravenously with 100 and 180 cm<sup>3</sup>, respectively, of heparin plasma obtained from Case 24 and Case 25, respectively, and filtered through a CHAMBERLAIN L 3. In three other cases the volunteers were given 100, 250 and 350 cm<sup>3</sup>, respectively, of heparinized whole blood from Cases 13, 23 and 26, respectively. In the first three cases mentioned, as well as the last case, nothing occurred during the 4 weeks of observation.

In the volunteer inoculated with blood from Case 23, however, the result was different. After an incubation period of about two weeks this individual developed the picture of a clinically, haematologically, serologically and pathologically typical infectious mononucleosis. An account of this case follows.

On February 22nd 1941, 250 cm<sup>3</sup> of heparinized venous blood from the clinically typical Case 23 (see case reports page 74) were transmitted to a healthy woman medical student K. U., 23 years of age, and of the blood group O. (The donor belonged to blood group O and her rectal temperature immediately before transfusion was 38.9° C). The subject of the experiment had on the whole always enjoyed good health and had never suffered from swollen lymph nodes. The blood count before the transfusion was normal (Table 14). The sedimentation rate was 6 mm/1 hr. The BUNNELL & PAUL test before transfusion gave no agglutination. The WASERMANN, M. B. R. II and KAHN tests were negative.

The result of the experiment may be seen in Table 14 and can be summarized as follows. From and including the fifth day after the transfusion, blood smears from the subject showed an increas-



TABLE 14. Transfusion to experimental subject K. U. of 250 cm<sup>3</sup> of heparinized blood from Case 23 with infectious mononucleosis.

TABLE 14. *Transfusion with infectious mononucleosis.*

Date	Total number of white blood cells	Blood count	Remarks				
		Polymorphonuclears	Mononuclears				
		Non-segm. %	Segm. %	Eosinophiles %	Lymphocytes %	Monocytoid and uncertain forms %	
21/2	5400	4	45	3.5	41	7.5	21/2 Before transfusion Bunnell & Paul no agglutination.
22/2	—	6	59	2	28	5	25/2 A number of lymphocytes show irregular nuclei.
24/2	—	9.5	50	3	32	5.5	3/3 Bunnell & Paul no agglutination.
25/2	—	9	44	5	37	5	5/3 The number of apparently pathological lymphocytes has obviously increased.
3/3	—	1	48	4	43	4	9/3 Sore throat. Tenderness behind angles of jaw. General malaise. Fever.
5/3	7600	1.5	48	3.5	46	1	10/3 Increased soreness of throat. Pharynx and tonsils reddened. The latter not enlarged.
7/3	9500	4	51	5	35	5	11/3 Considerable number of lymphocytes with irregular nuclei.
10/3	7400	11	47.5	1	34	6.5	12/3 General malaise aggravated. Soreness of throat also increased since yesterday. Tonsils larger. No necrotic foci.
11/3	5500	11	41	2	37.5	8	15/3 Tonsils intensely inflamed and almost meeting in the midline. Several necrotic foci up to the size of beans. Soft lymph nodes some as large as beans (2 under the mandible, 3—4 along the sternocleidomastoid, 2—3 pea-sized in each axilla and each inguinal region), all still present on 20/3. S. R. 8 mm/1 hr. Bunnell & Paul 1:32. Questionably palpable spleen.
12/3	4300	18	30	2	42	8	22/3 Sincars show numerous pathological lymphocytes (about 75 % of the lymphocytes counted) of the kind typical for infectious mononucleosis. Bunnell & Paul 1:32.
14/3	—	7	28	2	62	1	29/3 Symptoms receding. Throat better. Free of fever.
15/3	—	8	24	2	64	2	1/4 Angina cleared up. Persisting enlargement of lymph nodes, though no longer tender. Sincars still show numerous pathological lymphocytes.
17/3	5600	7	21	2	69	1	17/4 Enlarged lymph nodes and pathological lymphocytes as before.
20/3	—	5	31	1	62	1	13/5 Enlarged lymph nodes still persist, though smaller and not tender. Sincars still show pathological lymphocytes. Bunnell & Paul 1:32.
22/3	—	2	22	2	72	2	
27/3	7200	3	24	1	69	3	
29/3	—	4	33	2	58	3	
1/4	—	5	40	5	45	5	
4/4	—	4	34	3	56	3	
17/4	—	3	39	4	50	3	
13/5	3100	3	42	3	51	1	

ing number of pathological lymphocytes without the occurrence of any other clinical symptoms until the eighteenth day when increasing sore throat and a general malaise set in. On the twentieth day a rapidly developing relative lymphocytosis appeared and on the twenty-eighth day after the transfusion the blood picture showed 74 % mononuclear cells, including a large number of characteristic pathological lymphocytic elements (Table 14 and Figures 9 and 10). Concurrently the clinical picture had taken a typical course. The throat trouble increased while the tonsils became extremely tender and intensely inflamed and showed necrotic foci up to the size of beans. The patient had considerably difficulty in swallowing as well as a pronounced feeling of general malaise and fever. Palpation along the sternocleidomastoid muscles revealed a number of soft, slightly tender lymph nodes, some of which were as large as beans. Tender inflamed nodes that had not previously been observed were also found in the axillae and inguinal regions. After the lapse of one week and on about the thirty-fifth day after the transfusion, both the subjective and objective symptoms began to decrease rapidly. The swollen lymph nodes became nonsensitive and smaller. They were however still detectable when the subject was examined for control purposes three and twelve respective months later, on which occasions the blood count also still revealed distinct changes with 52 and 47 % respectively of mononuclear cells as well as pathological lympho-

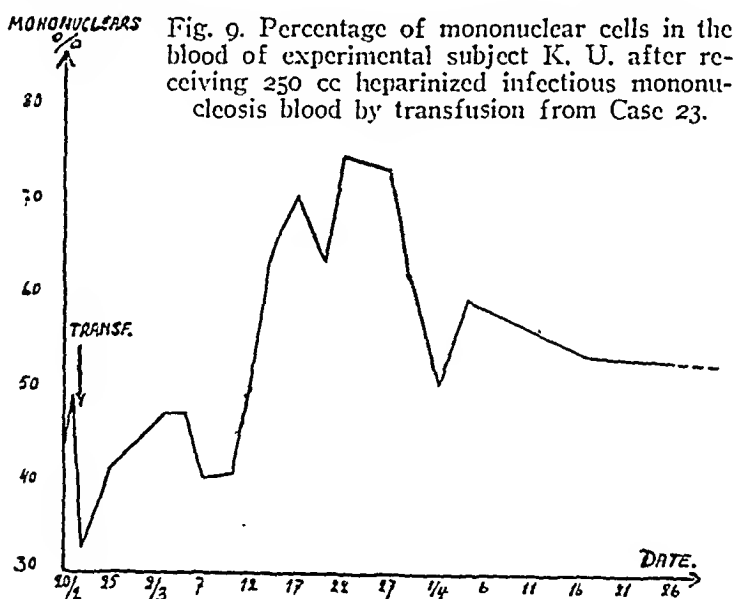


TABLE 15  
*The Davidsohn Differential Test for Infectious Mononucleosis in  
 Experimental Subject K. U.*

S e r u m	Agglutination in final dilution:				
	1:7	1:14	1:28	1:56	1:112
<i>Experimental subject K.U. (15/3/41)</i>					
Untreated serum .....	++	++	++	+	—
Serum, absorbed with guinea-pig kidney .....	++	++	+	±	—
Serum, absorbed with beef erythrocytes .....	—	—	—	—	—
<i>Experimental subject K.U. (20/2/42)</i>					
Untreated serum .....	+	±	—	—	—
Serum, absorbed with guinea-pig kidney .....	+	—	—	—	—
Serum, absorbed with beef erythrocytes .....	—	—	—	—	—

cytes with curiously shaped nuclei. In the donor the tests for sheep red cell agglutinins had reached a titer of 1:128 according to BUNNELL & PAUL. The same tests on the experimental subject before the transfusion and on the fourteenth day showed no agglutination and on the twentieth and twenty-seventh days a titer of 1:32. Thus neither donor nor experimental subject showed any very high hetero-agglutinin titer. In both however the titer rose during the course of the infection and moreover with the serum of experimental subject K. U. (Case 23 not tested) the DAVIDSOHN differential reaction was positive. (Table 15 below).

Sections were made of a lymph node excised from experimental subject K. U. on the sixtieth day after transfusion. The sections show marked reticulo-endothelial reaction with considerable hyperplasia and proliferation of the sinus endothelium. Among these are isolated lymphocytes and plasma cells as well as a not insignificant number of large mononuclear elements with nuclei not particularly rich in chromatin and in some instances kidney-shaped, probably constituting monocytes. There are also sparse numbers of polymorphonuclear leucocytes and an occasional eosinophil. In a number of follicles are seen well developed germinal centers. The lymph node is surrounded by a slightly thickened connective tissue capsule and even in the center of the node there is a good deal

of somewhat fibrous connective tissue. In the latter are sparse numbers of lymphocytes and occasional neutrophilic leucocytes. The histological picture corresponds well with that characteristic of the acute stage of infectious mononucleosis (Å. LINDGREN). The microphotographs of unstained sections at the absorption maximum of nucleic acid in ultraviolet light also show a microscopic picture indistinguishable from the fairly characteristic appearance of infectious mononucleosis nodes with the presence of a curious large-celled irregular hyperplasia (Figure 13).

Thus in this experimental subject, intravenously inoculated with heparinized blood from a case of infectious mononucleosis in the acute stage of the disease, there developed after an incubation period of eighteen days a clinical, haematological, serological and pathological disease picture indistinguishable from that of a typical case of infectious mononucleosis.

### 3. Microscopic examination of the human biopsy material.

Microscopic examination of biopsy material was done in 16 cases. In all of them (Cases 1—7, 13, 18, 20—24, 26—27) an enlarged lymph node was extirpated and in Cases 23, 24 and 25 a piece of tonsillar tissue was also removed. In Case 21 the extirpated lymph node was from the inguinal region but all the other biopsied nodes were from the cervical area. The nodes were excised from the 6th to the 18th day of the disease, that is during the still acute stage. (Table 1). All the lymph nodes presented a typical gross and microscopic appearance.

Grossly all of them were about as large as beans to hazel nuts, grayish-red in colour and strikingly soft in consistency with no inflammatory reaction in the surrounding tissues. The cut surface was spongy and bulging, finely granular and grayish-red in colour.

Microscopically all the nodes revealed the characteristic if not typical picture described by SPRUNT & EVANS, LONGCOPE, BALDRIDGE, ROHNER & HANSMANN, PRATT, DOWNEY & STASNEY and others.

The most characteristic feature perhaps is the extraordinary variety or irregularity in the microscopic picture in these lymph

nodes. The general architecture of the nodes is usually more or less lost (Fig. 14). It is replaced by a peculiar large-celled hyperplasia which often shows striking resemblance to the picture in HODGKIN'S disease, as has been pointed out by SPRUNT & EVANS, LONGCOPE, BALDRIDGE and collaborators and others. Occasionally there is punctate accumulation of lymphocytes which may sometimes resemble the picture in lymphatic leukemia. The general hyperplasia seems to be dominated by a proliferation of the reticulo-endothelial elements, especially in the region of the sinuses. The picture is that of a tissue composed predominantly of islands or strands of large clear cells with large irregular vesicular nuclei poor in chromatin. In addition there are large mononuclear cells with peculiar nuclei resembling the pathological lymphocytes in the blood. The blood and lymphatic vessels may be packed almost exclusively with large or small mononuclear cells. In preparations stained to demonstrate plasma cells there may be encountered numerous large and small cells with reddish granular protoplasm and rather deeply stained round nuclei. The smaller of these cells often show a definite "Radkern" nucleus. In some preparations the frequent occurrence of mitoses is striking. In none of the sections were any certain giant cells with more than two nuclei encountered. In Giemsa and toluidin blue<sup>1</sup> preparations there were mast cells along the capillary and vascular walls. Polymorphonuclear neutrophils and eosinophils occurred very sparsely.

Microscopic examination of sections from the tonsils in Case 24 (Fig. 15) revealed a picture similar to that described above. In Cases 23 and 24 there were only non-specific inflammatory changes with a profusion of lymphocytic elements.

In no cases were any bacteria found in direct smears of the lymph node suspension or in bits of lymph node pressed between cover slips and stained with methylene blue according to NEISSER, GRAM or ZIEHL-NIELSEN. Neither were any bacteria encountered in sections stained according to GRAM or GIEMSA.

In direct smears of lymph node material and also in Giemsa-

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<sup>1</sup> EHRLICH "Mastzellen" are stained by Holmgren and Wilander as follows: Fixation in 10 % formalin. Embedding as usual in paraffin. Staining for 1 hour in 1 % toluidin blue in 70 % alcohol. The deep reddish-violet of the heparin granules in the mast cells forms a beautiful contrast to the otherwise blue-tinged tissues.

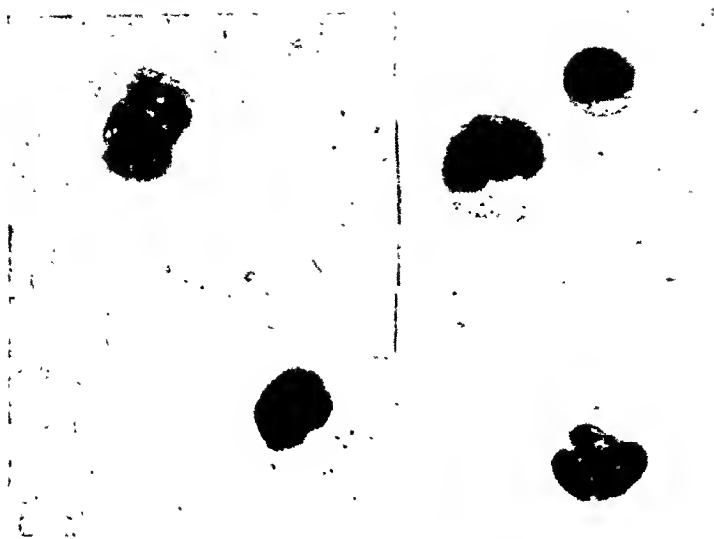


Fig. 10. Pathological lymphocytes in the blood of experimental subject K. U. the 30th day after transfusion of infectious mononucleosis blood. Giemsa. Photomicrograph  $\times 1200$ .



Fig. 11. Section from inguinal lymph node of experimental subject K. U. the 60th day after transfusion of infectious mononucleosis blood. Haematoxylin-eosin. Photomicrograph  $\times 75$ .

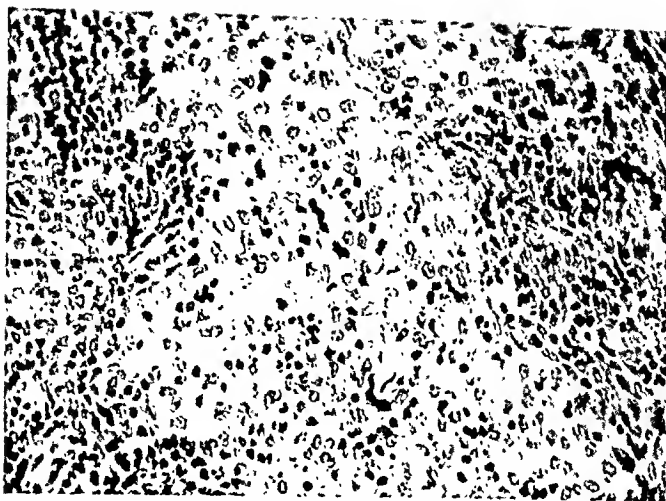


Fig. 12. Section from inguinal lymph node of experimental subject K. U. the 60th day after transfusion of infectious mononucleosis blood. Haematoxylin-eosin. Photomicrograph  $\times 400$

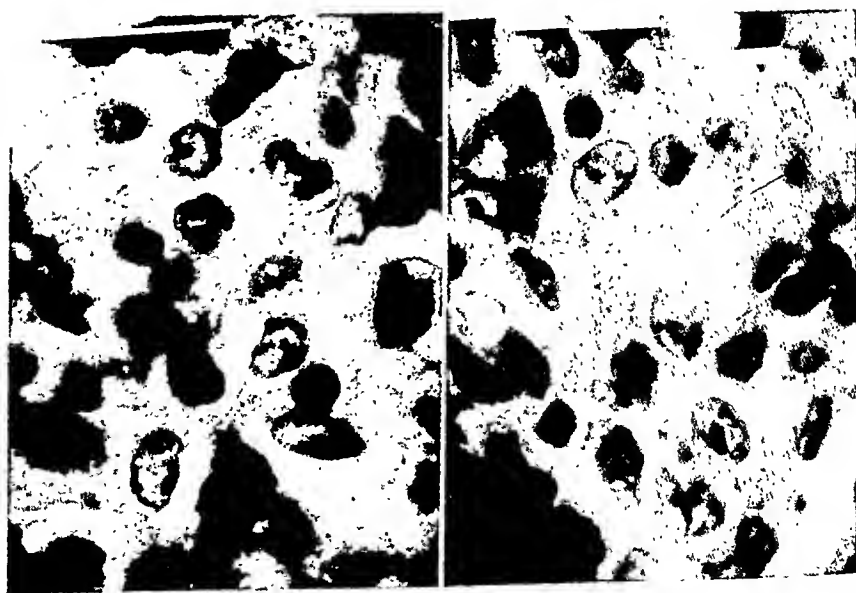


Fig. 13. Section from inguinal lymph node of experimental subject K. U. the 60th day after transfusion of infectious mononucleosis blood. Formol-fixed unstained section. Photomicrograph at  $2570 \text{ \AA}$ ,  $\times 1190$ .

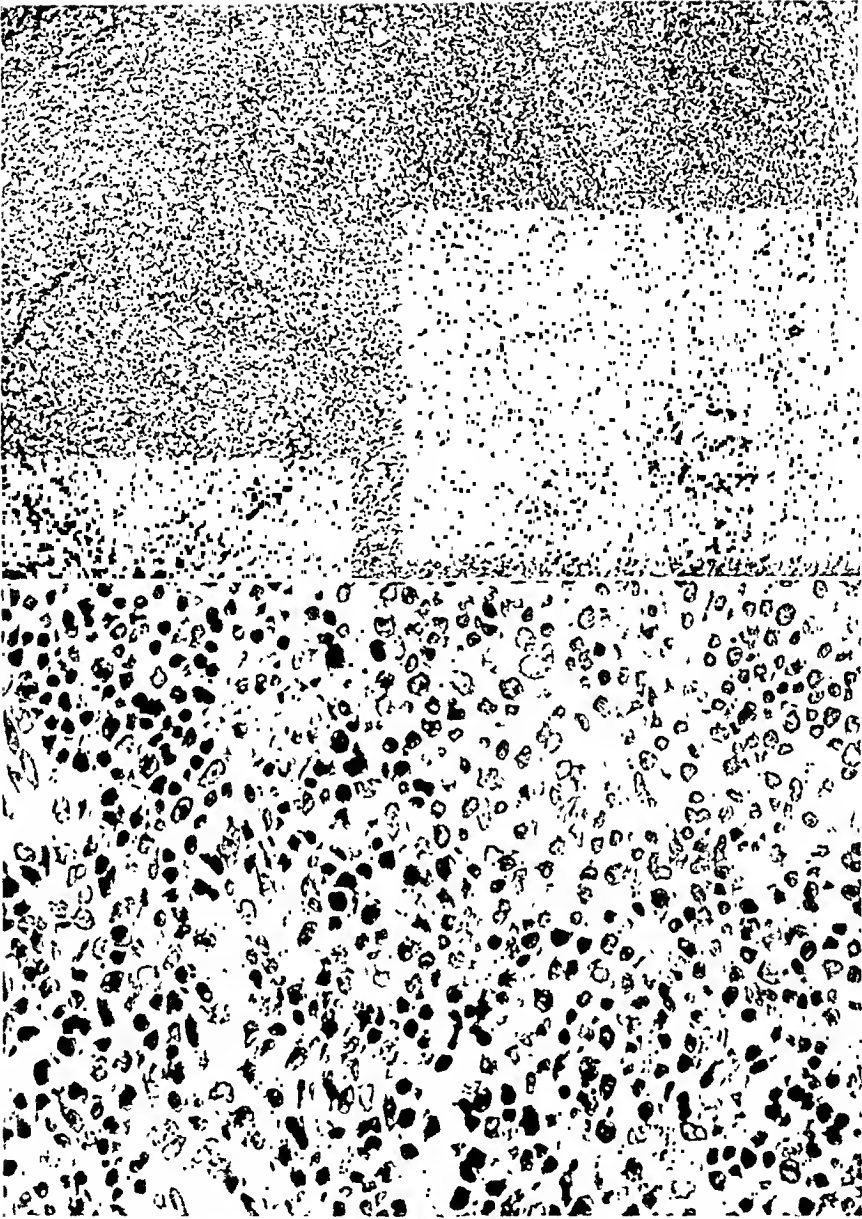


Fig. 1. a and b. Sections from human cervical lymph nodes showing typical picture in infectious mononucleosis. Complete obliteration of the normal follicular architecture. Diffuse pleomorphic hyperplasia. Haematoxylin-eosin. Photomicrographs, a  $\times 60$  (Case 13) b  $\times 380$  (Case 4).



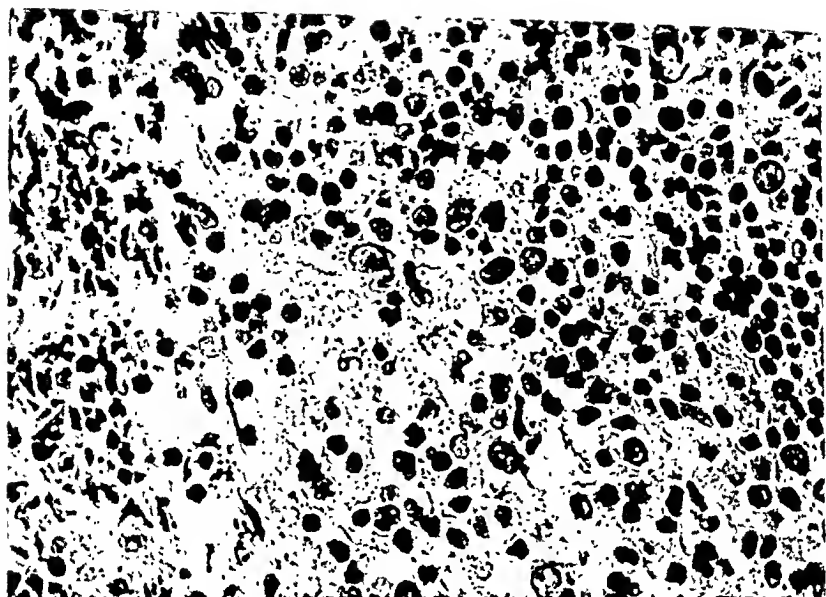


Fig. 15. Section from human tonsil in infectious mononucleosis (Case 24), Haematoxylin-eosin. Photomicrograph  $\times 900$ .

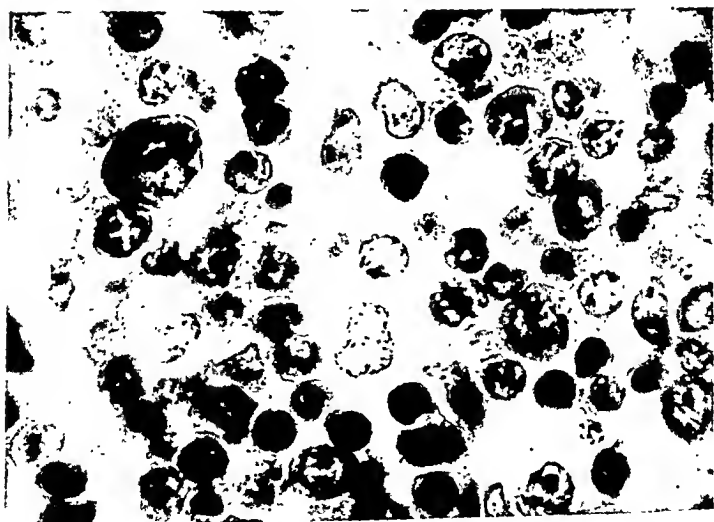


Fig. 16. Cervical lymph node from Case 23 with infectious mononucleosis. Formol-fixed unstained section. Photomicrograph at  $2570 \text{ \AA}$ ,  $\times 1220$ .

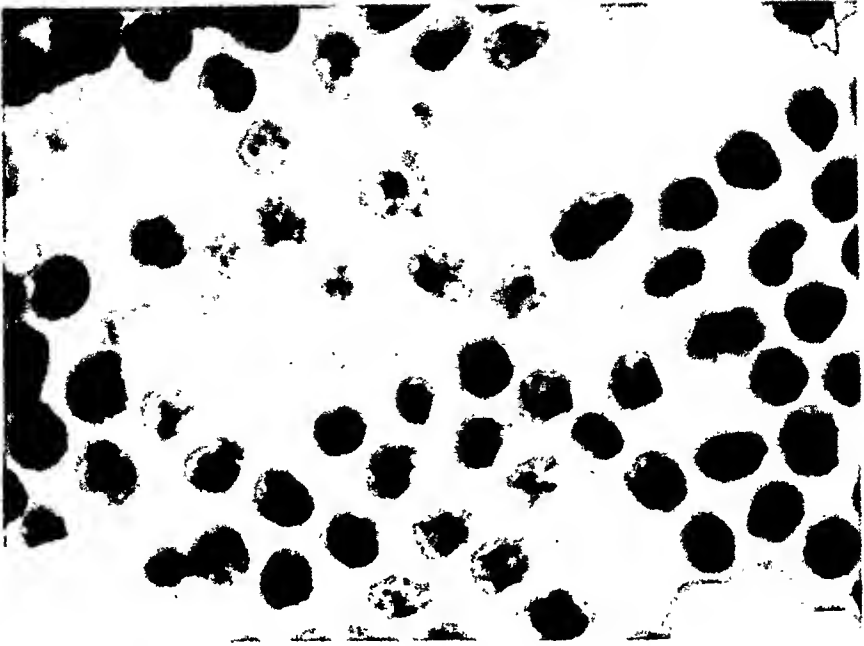


Fig. 17. Normal human lymph node. Unfixed unstained smear, Photomicrograph at 2570 Å,  $\times 1190$ .

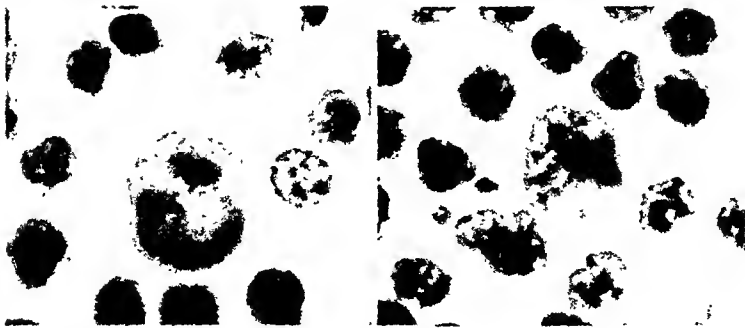


Fig. 18a and b. Cervical lymph node from Case 24 with infectious mononucleosis. In the center of both pictures are large cells with cytoplasm showing very marked ultraviolet absorption indicative of massive presence of cytoplasmic nucleic acids. Unfixed, unstained fresh smear. Photomicrographs at 2570 Å,  $\times 1220$ .

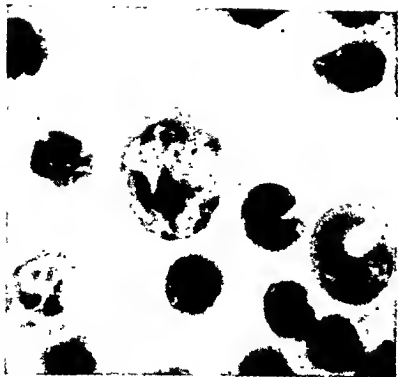


Fig. 19. Cervical lymph node from Case 24 with infectious mononucleosis. Large cell with giant nucleolus surrounded by chromatin. Irregularities in the markedly ultraviolet absorbing cytoplasm. Unfixed, unstained fresh smear. Photomicrograph at 2570 Å,  $\times 1220$ .



Fig. 20. Cervical lymph node from Case 24 with infectious mononucleosis. In the center of the picture is a large cell with pronounced derangement of the nucleolus mechanism. Irregular distribution of nucleotides in the cytoplasm with granular foci showing strikingly slight ultraviolet absorption, surrounded by a halo of marked such. Unfixed unstained fresh smear. Photomicrograph at 2570 Å,  $\times 1220$ .

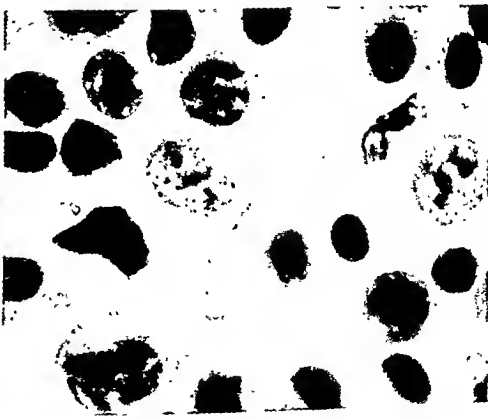


Fig. 21 a and b. Cervical lymph node from case 24 with infectious mononucleosis. In the center of both pictures are large cells with markedly ultraviolet-absorbing cytoplasm. In the cytoplasm are granular foci showing especially intensive absorption and surrounded by halo-like zones of remarkably little such. Considerable accumulation of nucleotides close to the nucleolus. Unfixed unstained fresh smears. Photomicrographs at 2570 Å,  $\times 1220$ .



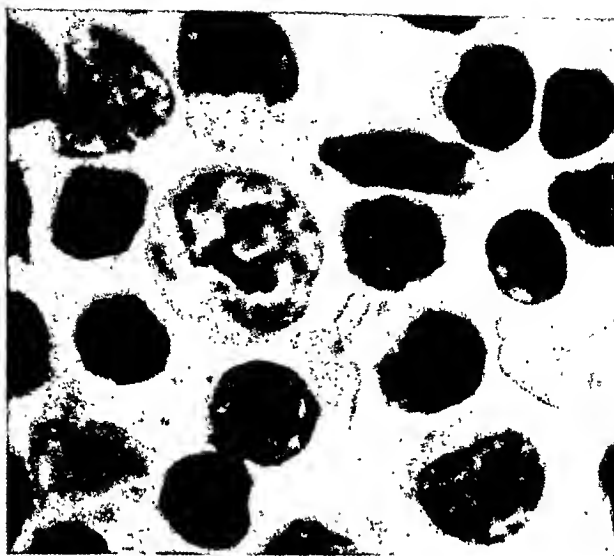


Fig. 24. Cervical lymph node from Case 27 with infectious mononucleosis. Several large cells with granular foci in the cytoplasm. In the large cell toward the center of the upper border of the picture there are punctate foci showing intense ultraviolet absorption surrounded by a halo with little absorption. Unfixed unstained fresh smear. Photomicrograph at 2570 Å,  $\times 2440$ .

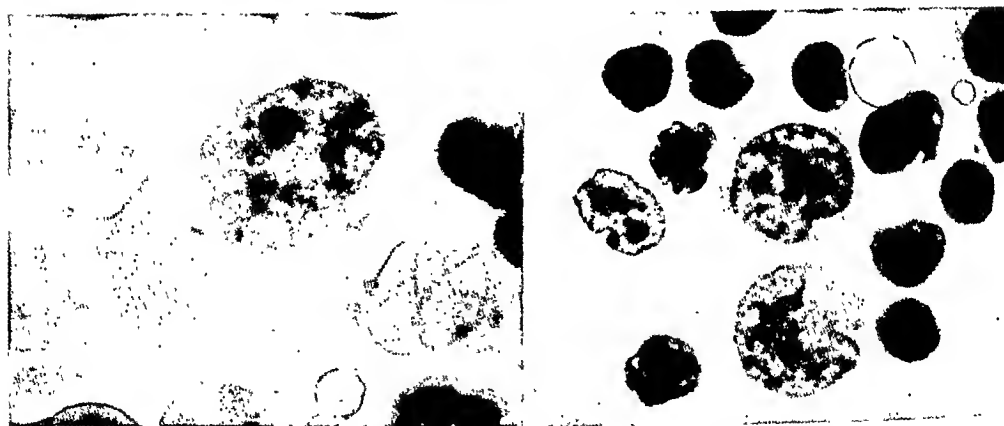


Fig. 25 a and b. Cervical lymph node from Case 27 with infectious mononucleosis. Large cells with granular irregularities in the intensely ultraviolet-absorbing cytoplasm. The contours of the nuclear membranes are outstanding due to the accumulation of nucleotides close to them. Unfixed unstained fresh smear. Photomicrograph at 2570 Å,  $\times 2440$ .

stained sections a number of preparations seemed to reveal punctiform, predominantly intracellular, granular structures of uniform size, when high magnification (1400—1600  $\times$ ) was used. For this reason attempts were made to stain with Victoria blue 4 R concentrated (GRÜBLER-HOLBORN) according to HERZBERG. In order to localize any possible granules to certain cell types it seemed desirable to use thin sections. As the literature contained no description of how to stain tissue sections with Victoria blue, an attempt was made according to PÖTTER's modification of the WEIGERT neuroglia stain.<sup>1</sup>

Sections suitably stained according to this technique showed moderately deep staining of the nuclei and a pale bluish protoplasm. The heparin granules of the EURLICH "Mastzellen" assumed a dark violet metachromatic tone. In preparations from a number of lymph nodes some of the large cells presented small violet granules sometimes surrounded by a lighter halo. As however heparin obviously to some extent gives metachromasia with Victoria blue; also demonstrated in experiments in vitro, the structures observed with this technique could not with certainty be differentiated from heparin granules. The sections presented otherwise only the picture seen in haematoxylin-eosin sections. In no preparations were there observed any morphological structures which could be interpreted as microorganisms of bacterial nature.

Ultraviolet light photography for the study of viruses seems to have been used since 1922—23 when Frosch appears to have been the first to use this method in a study on the bovine pleuro-pneumonia virus. He used the technique described by Köhler with the 2750 Å line of cadmium as his light source. Barnard, who has made the most notable contributions in this field also generally used  $\lambda = 2750$  Å, but recently he has reported having obtained very promising results with  $\lambda = 2530$  Å (Elford). Viruses and bacteria, however, like all living organisms engaged in rapid re-

<sup>1</sup> SCHIMORI-GEIPEL. Die pathologisch-histologischen Untersuchungsmethoden, C. W. Vogel, Berlin, 16th Edition, 1934, page 298. Fixation in 5—10 % formol and embedding in paraffin. Staining in concentrated aqueous solution of Victoria blue 4 R, concentrated (Grübler-Holborn) for 72 hours. The sections are dried cautiously with a filter paper moistened in Lugol's solution to which they are transferred for a second. After drying with finely granular, moist filter paper, differentiation is carried out in aniline-xylol 1:5. The differentiation is controlled under a microscope and stopped when the desired intensity has been attained. Careful washing in xylol and mounting in *neutral* Canada balsam.

production are characterized by their high content of nucleic acids (CASPERSSON). The nucleic acids which to no less than one-third of their molecular weight consist of purine and pyrimidine bases present, due to the pyrimidine ring, a strikingly intensive selective absorption of ultraviolet rays around 2600 Å (SORET, HARTLEY, DHÉRÉ, MARCHLEWSKI, HEYROTH & LOOFBOUROW, CASPERSSON, all cited by CASPERSSON). Thus the taking of microphotographs at the nucleic-acid absorption maximum in the ultraviolet would seem to provide not merely the possibility of further analysis of even unstained tissues and therefore of tissues unaffected by chemical agents but also of course the attainment of the somewhat more than doubled power of resolution in microscopy which the use of the short wave light implies. BARNARD (1937) in a comparative study of the viruses of foot-and-mouth disease and visicular stomatitis in an extensive series of ultraviolet photographs used  $\lambda = 2570 \text{ Å}$  (ELFORD). Ultraviolet light photography seems hitherto not to have been used in the study of infectious mononucleosis.

Therefore in a number of cases microphotographs were made of unstained lymph node tissue at the nucleic-acid absorption maximum in the ultraviolet using the technique which CASPERSSON has worked out on the basis of KÖHLER's procedure. A detailed description of this method is to be found in CASPERSSON's original papers to which the interested reader is referred. The procedure is based on access to a microscopic apparatus of exceedingly high quality where all the optical systems involved are made of molten quartz. The source of light is a spark between rotating electrodes in the form KÖHLER has devised for his ultraviolet microscope.

All microphotographs in ultraviolet light in the present study were taken at the nucleic-acid absorption maximum in monochromatic light of wave length 2570 Å. In Cases 1—7 and 23, about five  $\mu$  thick sections of formol-fixed paraffin-embedded lymph nodes were examined. In Cases 21 and 22 sections of lymph nodes treated according to the GERSH freezing-drying method were studied. In Cases 24, 26 and 27 fresh smear preparations were examined in direct connection with the extirpation of the respective lymph nodes.

The microphotographs obtained present consistent pictures. Detailed analysis of the finest cytological structures turned out to

be possible only in preparations from Cases 24, 26 and 27 in which the photographs had been taken in immediate connection with the lymph node extirpation and with a short exposure of smears made by as gentle technique as possible. Pictures obtained in the latter way may most certainly with justification be said to reveal the habitus of the living tissue.

The microphotographs show, besides masses of lymphocytes and plasma cells, the previously mentioned numerous large cells of varying diameter. These latter cells exhibit for the most part very intensely absorbing cytoplasm (at  $2570 \text{ \AA}$ ) indicative of the presence of large quantities of cytoplasmic nucleic acids (Figures 18—25). The nuclear membranes often seem to stand out due to the assemblage of nucleotides close to them (Figure 19, 21, 22, 25). The nucleoli are often strikingly large and irregular and surrounded by irregular zones of chromatin (Figures 19 and 21 a). There is frequently marked disarrangement of the nucleolus mechanism (Figure 20). Moreover the numerous large cells show almost constantly striking irregularities in the cytoplasm which often contains punctiform foci with intense ultraviolet absorption and surrounded by a narrow lighter halo (Figures 21 and 24). In other cases there are granular foci with extremely little ultraviolet absorption, and showing an intense contrast to a halo-like zone of deep absorption (Figures 20, 22, 23).

In no preparation was it possible to observe any structures which could be interpreted as microorganisms of bacterial nature.

The above-described changes were found in all the examined lymph nodes extirpated from cases of infectious mononucleosis and in no nodes from the controls. Similar technique was used and examined were normal lymph nodes from two otherwise healthy persons, who happened to be operated upon for varices and a praesacral lymph node without pathological changes from a patient with cancer of the rectum and removed at the operation for the cancer. In addition there were examined lymph nodes with moderate non-specific inflammatory lesions, extirpated from the inguinal region from four patients in connection with operations and lastly a large cervical lymph node which turned out to show tuberculosis microscopically.



### III. DISCUSSION

A discussion of the results of the present investigation would seem to indicate the following.

First of all that a basis for the assumption of an etiological connection between infectious mononucleosis in man and any pathogenic agent of bacterial nature could not be demonstrated. The thirty blood cultures which were taken during the initial highly febrile stage of the disease and cultivated under aerobic as well as anaerobic conditions gave in every instance negative results. Smear preparations and sections from the enlarged lymph nodes extirpated from 16 patients in the acute stage of the disease and stained according to current methods or photographed at the nucleic-acid absorption maximum in ultraviolet light did not reveal any morphological structures which could be interpreted as microorganisms of bacterial nature. Cultures from the same lymph nodes, carried out under aerobic and anaerobic conditions, were also negative. The sparse growth of *B. Friedländer* in one case as well as the occasional occurrence of staphylococci and diphtheroids in single substrates would undoubtedly seem to be regardable as insignificant, not merely in view of the facts just mentioned but also in consideration of the frequent occurrence of the latter bacteria in lymph nodes in all kinds of disease conditions (FRAENKEL & MUCH, BLOOMFIELD, HARRIS & WADE, BERGSTRAND and others).

It would seem as if the question of the connection postulated by NYFELDT between bacteria of the *Listerella* family (*Listerella monocytogenes hominis* Nyfeldt) and infectious mononucleosis in man should be scrutinized in more detail. The fact that *Listerella* do produce specific infections in animals as well as in man seems obviously well established by studies of the spontaneous diseases in question and their experimental reproduction by several workers. The fact that such infections are widely and frequently distributed in animals suggests, however, that *Listerellosis* is essentially an affliction of animals (*Julianelle*). Infection with *Listerella* would seem to have

been first described by MURRAY, WEBB & SWANN in connection with an epidemic in stock laboratory rabbits. Since then epidemics have been reported by PIRIE in gerbilles (*Taterona lobengula*) and by GILL, JUNGHERR, GRAHAM and his collaborators, MORIN, BIES-TER & SCHWARTE, PATERSON, JONES & LITTLE in sheep and cattle. CROMWELL and his collaborators described an epidemic in silver foxes. The clinical course of *Listerella* infection in monkeys has been recounted by BURN and SEASTONE among others. *Listerellosis* has also been observed in poultry by TEN BROECK, PATERSON, SEASTONE and others.

In rodents *Listerellosis* seems to present the picture of a septic infection and autopsy reveals multiple necrotic foci in the liver as the most characteristic feature. In the higher mammals a more or less purulent meningitis or meningoencephalitis seems to dominate the clinical and microscopic picture. Rodents are the only animals where a definite mononucleosis seems to occur (MURRAY, WEBB & SWANN, NYFELDT, SEASTONE, MORRIS and JULIA-NELLE). In higher animals the common polymorphonuclear infective response of the blood picture is the only change that has been recorded in *Listerella* infection (GILL, JUNGHERR, GRAHAM, HESTER & LEVINE).

The writer's experiments on the inoculation of the Nyfeldt strains "28" and "37" into rabbits gave the result that possibly one of the eleven animals showed a slight transient increase in the percentage of mononuclear cells in the blood. Otherwise there was observed only moderate leucocytosis without a significant change in the mutual proportion between polymorphonuclear and mononuclear cells in the blood. Although the blood of the experimental animals shortly after the inoculation showed young and monocytoid mononuclear cells to a large extent, this circumstance should not be ascribed decisive significance in view of the fact that Bland has described the same change after inoculation with the Pasteur Institute type strain of *Toxoplasma cuniculi* as well as in consideration of the obvious general lability of the blood picture in rabbits. In the experiments where the same Nyfeldt strains were used on monkeys, the result was a severe septicaemia with meningitis and encephalomeningitis as the predominant symptoms along with a polymorphonuclear leucocytosis. Thus we can only verify (1) the correspondence of the clinical and pathological disease picture

TABLE 16.  
Fatality of *Listerella* Meningitis in Man.

Observer	Date	Location	Number of Patients	
			Re-reported	Died
Atkinson .....	1917	Australia .....	5	4
Tesdal .....	1934	Sweden .....	1	1
Schultz et al. ....	1934	California, U. S. A. ...	1	0
Burn .....	1934	Connecticut, U. S. A....	4	4
Allen <sup>1</sup> .....	1936	Connecticut, U. S. A....	1	1
Gibson .....	1936	Scotland .....	1	0
Carey .....	1936	Massachusetts, U. S. A.	1	0
Poston et al. ....	1937	N. Carolina, U. S. A.	1	1
Wright and MacGregor	1938	Scotland .....	1	1
Cislaghi <sup>2</sup> .....	1938	Italy .....	1	0
Porter and Hale <sup>3</sup> ....	1939	Iowa, U. S. A. ....	1	0
Porzecanski and de Baygorria .....	1939	Uruguay .....	1	0
Totals			19	12

<sup>1</sup> This case cited by Burn.

<sup>2</sup> Not verified by bacteriological study.

<sup>3</sup> Treated with sulfanilamide, possibly responsible for recovery. (Cited by Julianelle, L. A.: Ann. Int. Med. 14,614, 1940.)

arising in the two types of animal mentioned and that described in the literature as more or less typical of infection with bacteria of the *Listerella* family, and (2) the absence of similarity to infectious mononucleosis in man.

Of more interest in this connection however, seems the probable distribution of *Listerellosis* in man. There can be no doubt that although the pathway of infection is still obscure, there is increasing recognition of the occurrence in man of a *Listerella* purulent meningitis which, while not so fatal as for instance the pneumococcal or staphylococcal varieties, does have a high mortality rate (JULIANELLE). Table 16 above gives a survey of the not inconsiderable number of papers reporting cases where the diagnosis of *Listerellosis* seems to have been well founded bacteriologically.<sup>1</sup>

<sup>1</sup> Excluding the case of Cislaghi which was not bacteriologically verified and was most certainly not *Listerellosis*.

A more detailed analysis of the material cited above shows that the human cases of the disease which could be associated with *Listerella* infection have involved predominantly the youngest year groups and that the clinical and pathological disease picture has been in all cases remarkably uniform.<sup>1</sup> Clearly *Listerella* infection in man seems on the whole to present a picture identical with that described for higher mammals, including monkeys, when infected with this family of bacteria. Thus the disease seems to proceed with the picture of a severe septic infection and a more or less purulent meningitis or meningoencephalitis as the predominant symptoms. The mortality in the material described was as high as 70 %. In no case are lymph node enlargements reported. There seems to have been no difficulty in the demonstration of the bacteria in direct smears and in cultures of the cerebrospinal fluid or in blood cultures from the patients. Unfortunately it would seem as if blood counts and serological tests have been undertaken only exceptionally. Those workers who however do report the results of such examinations have not on any occasion observed any increase in the occurrence of mononuclear cells in the blood of their patients (CAREY; POSTON, UPCHURCH & BOOTH; PORZECANSKI & DE BAYGORRIA). There was observed, however, agglutination of the homologous *Listerella* strain (CAREY). None of the papers from which the *Listerellosis* material in Table 16 is derived contain any report of increased occurrence of hetero-agglutinins in the serum of the patients.

If we regard the results of the writer's experiments in the light of the above, it would first of all seem as if stress should be laid on the fact that on no occasion was there obtained significant growth of bacteria, either in 30 blood cultures or in the cultures of material from the 16 extirpated lymphomas, although all these investigations were carried out during the acute febrile stage of the disease and with the observance of all precautions.

If we consider the results of the serological experiments (Page 30) it becomes obvious that immune bodies against the Nyfeldt *Listerella* strains "28" and "37" could not be demonstrated in any greater quantity in patients who had just recovered from infectious mononucleosis than in the healthy controls. Cuta-

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<sup>1</sup> Excluding the case of Cislighi which was not bacteriologically verified and was most certainly not *Listerellosis*.

neous tests, intravenous injection of antigen, examination for the presence of agglutinins and the flocculation reaction according to MÜLLER-WASSÉN were all performed. Antisera against the Nyfeldt *Listerella* strains were developed and obtained from healthy medical students. These antisera with a high agglutinin titer and positive flocculation reaction with homologous antigen according to MÜLLER-WASSÉN turned out when tested according to BUNNELL & PAUL not to contain agglutinins against sheep red blood cells in a titer higher than that found normally.

These results point in the same direction as those recently obtained in animal experiments by other investigators. PISU showed that the sera of rabbits immunized with *B. monocytogenes* MURRAY and *B. monocytogenes hominis* NYFELDT (Lister Institute Type Culture 5105) did not agglutinate sheep red blood cells. KOLMER, also in experiments on rabbits, showed that *Listerella* strains, including that of MURRAY, WEBB & SWANN, though promptly producing complement-fixing antibody and agglutinins for antigens of homologous strains, did not produce either complement-fixing reagins for the antigens commonly employed in the sero-diagnosis of syphilis or agglutinins for sheep erythrocytes. Although PONS & JULIANELLE obtained growth of a diphtheroid, in all probability of the *Listerella* family, in the blood culture in one out of seventeen cases of infectious mononucleosis, JULIANELLE points out that the bacterium in question was *not* agglutinated by the serum of the patient and that there are serious objections to the existence of any genuine relationship between *Listerella monocytogenes* and the disease mentioned since twenty-two strains of *Listerella*, seven of which were of human origin, proved in rabbit experiments their inability to stimulate the formation of heterophilic antibodies, either on prolonged immunization or by active infection in animals responding to the bacterium with high agglutinin titers. Moreover rabbit anti-sheep and anti-heterophilic sera did not cause agglutination of their *Listerella* strains. Recently JANEWAY & DAMMIN stated that *Listerella* agglutination tests with the sera from thirteen cases of infectious mononucleosis, though in some cases probably giving a slightly elevated titer as compared with that of the control sera, showed no trend upward or downward in the *Listerella* agglutinin titer during the course of the disease or recovery from it. Seven *Listerella* strains had been tested, two of them from human cases of

meningitis. JANEWAY & DAMMIN conclude that etiological relationship between the known *Listerella* organisms and infectious mononucleosis is hardly suggested by their results.

The by now rather conclusively demonstrated inability of *Listerella* monocytogenes to stimulate the formation of heterophilic antibodies, either by prolonged immunization or by active infection in man or animals, as well as the absence of immune bodies against this bacterium in the sera of human infectious mononucleosis convalescents, together constitute the most serious objection to the existence of any relationship between *Listerella* monocytogenes and infectious mononucleosis.

As a conclusion to what has already been said, the following statement would seem justified. The obviously extreme contrasts between the clinical and pathological disease picture in known cases of animal and human *Listerella* infection and human infectious mononucleosis, taken in conjunction with the results of the present and previous bacteriological, serological and animal experiments as well as the writer's experiments with human material would all seem to speak categorically against the possibility of any pathogenetic connection between human infectious mononucleosis and any hitherto known bacterium of the *Listerella* family.

The reason why this problem has been dealt with in such detail is the fact that the literature of recent years, even that of the handbooks, contains references to Nyfeldt's view as to the existence of such a connection, despite the previous absence of control investigations on this subject.

In the introduction to this paper were mentioned a number of experiments by JOHN BLAND. This investigator by inoculating citrated blood from a case of infectious mononucleosis had produced in rabbits an indefinitely passagable disease, clinically and pathologically indistinguishable from the characteristic disease picture of rabbit Toxoplasmosis, including the presence of Toxoplasms in the organs of the animals. Blood from infected rabbits when injected into monkeys caused a rise in the percentage of the mononuclear cells in the blood.

In view of the many and pronounced differences in the clinical course as well as in the pathological picture in human infectious mononucleosis and Toxoplasmosis of animals and taking into con-

sideration the common occurrence of even fatal nosocomial protozoal infections in rabbits, it would seem a priori as if BLAND's assumption of the significance of *Toxoplasma cuniculi* for the etiology of Pfeiffer's disease was rather unlikely. It might be assumed that a latent Toxoplasmic infection appeared or was started in his first rabbit and that passage increased the virulence of the strain enough to make it pathogenic for monkeys. On the other hand a specific agent may have been transferred with the protozoa. The fact remains that Bland succeeded in producing a mononuclear blood picture in monkeys and this seemed to justify the writer's repetition of the experiments as a control. Heparinized blood from ten patients in the acute febrile stage of infectious mononucleosis was inoculated intravenously into rabbits but failed to produce any changes whatsoever, either clinically or haematologically in the eight animals which survived the primary interference. Thus Bland's results could not be confirmed. In this connection it would seem of interest that *Toxoplasma* of human and animal origin have been shown by SABIN & OLITSKY to be biologically identical in their pathogenicity for mammals and birds, and immunologically by producing an active immunity against one another and by the fact that a serum against one neutralizes both. They have furthermore demonstrated that the sera of monkeys recovering from experimental Toxoplasmosis could be shown to contain neutralizing antibodies for parasites while the sera of a number of infectious mononucleosis convalescents revealed no such antibodies.

It may thus be concluded that no evidence has as yet been brought forward which is indicative of the existence of an etiological relationship between organisms of protozoal nature and human infectious mononucleosis.

Thus if the inoculation experiments on rabbits turned out negatively, it would still probably seem justified to interpret the experiments on monkeys as the successful transmission of the disease to this animal. The fact remains that fresh lymph node suspensions (sterility test on common substrates negative) obtained from a number of patients with infectious mononucleosis during the acute stage of the disease and inoculated into monkeys in three instances, produced, after an incubation period of from eight to nineteen days, mild clinical symptoms including general lymph node enlargement and an increase in the percentage of mononuclear cells in the blood

and that a reproduction of the condition seems to have been obtained in respectively five, three and two subsequent passages. Moreover sections from the lymph nodes of the monkeys mentioned showed a microscopic picture closely similar to that of lymph nodes in human infectious mononucleosis while this picture was absent in the lymph nodes of a number of control monkeys.

In regard to the experiments on passage to human beings, there seems scarcely any doubt that the disease was successfully transferred to experimental subject K. U. The disease picture which she presented was in all respects typical, clinically and haematologically as well as microscopically in the sections of the extirpated lymph node. Although Case 23 as well as K. U. presented a heteroagglutinin titer below 1:256 when tested according to BUNNELL & PAUL, the result of Davidsohn's differential test may be regarded as unequivocal proof of the diagnosis in the light of the remaining facts. It may perhaps be worth while mentioning in this connection that only 60—80 % of cases of infectious mononucleosis agglutinate sheep erythrocytes in a titer of 1:256 or over (OLESEN, BANG & KRISTENSEN, THOMSEN, ØLLGAARD among others). The circumstance that both aerobic as well as anaerobic cultivation gave a negative result with the blood with which the passage had been obtained, seems to deserve further mention.

Lastly if a survey is made of the results of the microscopic examination of the human biopsy material it would seem as if the following points should be stressed. Sections of all the nodes showed the characteristic if perhaps not typical picture of a pleomorphic large-celled hyperplasia as has been described by SPRUNT & EVANS, LONGCOPE, BALDRIDGE, ROHNER & HANSMANN, PRATT, DOWNEY & STASNEY and others. The results of previous investigators could thus only be confirmed. Pieces of tonsillar tissue were excised in three cases. In two instances the tissue showed only the non-typical picture, rich in mononuclear cells, described by Fox. In sections from the tonsil of the third patient there were in addition areas dominated by irregular, large, clear cells reminiscent of the microscopic picture in the lymph nodes as in one of the cases published by FAHLÉN.

The microphotographs taken at the nucleic-acid absorption maximum in ultraviolet light showed that the frequently mentioned large cells of varying diameter, more or less distinctive of the micro-



scopic picture of the lymph nodes in infectious mononucleosis, present in great number a cytoplasm with very intense absorption (at 2570 Å), indicating the presence of large amounts of cytoplasmic nucleic acids (Figures 18—25). These cells also commonly reveal irregularities in the cytoplasm, often in connection with granular foci showing marked ultraviolet absorption and surrounded by halo-like zones of strikingly little absorption (Figures 21 and 24), and sometimes similar punctate foci of only slight ultraviolet absorption surrounded by zones of intense absorption (Figures 20, 22, 23). These punctate foci are constantly of about the same size in the different cells of the same lymph node as well as in the lymph nodes from different cases of infectious mononucleosis. The nuclear membranes often seem to stand out prominently and the nucleoli are strikingly large and irregular, usually surrounded by irregular zones of chromatin (Figures 19, 21 a). Certain parts of the chromatin, probably corresponding to the heterochromatic portion, seem thus to form large masses of nucleolar substance and to persist as a clearly distinct zone around the nucleoli (Figure 21 a). The latter induce the formation of cytoplasmic nucleic acids and cytoplasmic protein at the nuclear membrane. All the phases in this process can be distinctly observed in different examples of these large cells which thus present according to CASPERSSON all the characteristic features of cells which have been irritated to vigorous growth but not to division and giving the picture of a system of protein formation stimulated to intense activity. The appearance of the nucleolar apparatus as well as that of the nuclear membrane and the discontinuous distribution of nucleotides in the cytoplasm of the large cells must be regarded as evidence of pronounced disturbance in the cytochemical mechanism. At present it would not seem possible to decide with certainty whether or not the strikingly high nucleic-acid content of the cytoplasm of these large cells could conceivably be interpreted as due to the presence of virus, a conception which does not seem improbable, and whether in such case the irregularities and the observed granular phenomena could be conceived of as evidence of different stages of generation or whether the phenomena in question are only an expression of a mechanism of protein formation which is functioning pathologically. Thus even if the question of the probable virus nature of the cellular changes observed in the lymph nodes of

patients with infectious mononucleosis must be left to future research to provide a definitive answer, there remains the fact that similar cellular pictures have on no occasion been observed in the control material. Neither did CASPERSSON ever observe similar cytoplasmic phenomena in normal or cancer cells.<sup>1</sup>

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<sup>1</sup> Personal communication.

## IV. SUMMARY

1. Twenty-seven sporadic cases of infectious mononucleosis (Pfeiffer's disease), all clinically, haematologically and serologically typical, were studied from the etiological point of view.

2. Thirty blood cultures from twenty-one cases of the disease in the acute febrile stage were negative on incubation under aerobic and anaerobic conditions.

3. Aerobic and anaerobic cultures of lymph node tissue were negative in material from sixteen cases of the disease in the acute febrile stage.

4. The question of a possible pathogenetic connection between *Listerella monocytogenes hominis* NYFELDT and human infectious mononucleosis was the object of analysis in a number of experiments. Used were two strains of the bacterium in question (obtained from NYFELDT himself) called "28" and "37" and stated to have been obtained in blood cultures from typical cases of the disease.

On intravenous injection into rabbits these bacteria caused an increase in the "monocytoid" cells in the blood. A percentual increase of mononuclear cells was observed in one of eleven experimental animals. In no case during the period of observation or at autopsy on the animals was any lymph node enlargement or other macroscopic change encountered. The blood picture in the animals in question showed, as in NYFELDT's material, striking variation in the values obtained at examination on consecutive occasions. It did not seem possible to differentiate these morphological changes in the blood from those described by MURRAY, WEBB & SWANN in connection with *Listerella* infection or those reported by BLAND in connection with the inoculation of the Pasteur Institute typestrain of *Toxoplasma cuniculi*.

Intravenous inoculation of the NYFELDT strains into two *Macacus rhesus* monkeys produced a rapidly lethal infection with suppurative meningitis and encephalitis. Reaction from the lymphatic system in the form of lymph node enlargement, lymphocytosis or the

occurrence of pathological lymphocytes or monocytic cells in the blood could not be demonstrated. The disease picture which was obtained seemed to correspond well with that described by several workers (BURN, SEASTONE, JULIANELLE) as typical of infection of higher mammals with strains of the *Listerella* family, as well as with the symptom complex reported by a number of investigators (reviewed by JULIANELLE) in cases of what seemed to be undoubted *Listerella* infection in man. Significant, clinical, haematological or pathological similarities between the disease picture produced with the NYFELDT strains in monkeys and infectious mononucleosis in man could not be shown. On cutaneous testing, intravenous injection of antigen and examination for the presence of agglutinins or the flocculation test according to MÜLLER-WASSÉN, immune bodies against the NYFELDT strains could not be demonstrated in patients who had just recovered from infectious mononucleosis to any greater extent than in healthy controls. Human antisera (against the NYFELDT strains) with high agglutinin titers and a positive flocculation reaction in accordance with MÜLLER-WASSÉN turned out when tested according to BUNNEL & PAUL not to contain sheep erythrocyte agglutinins in a higher titer than that occurring normally.

5. In eight cases attempts to transmit the disease to rabbits by intravenous inoculation of heparinized blood from patients in the acute febrile stage of infectious mononucleosis were negative. Thus the assumption of BLAND as to the significance of a *Toxoplasma* for the pathogenesis of the disease could not be confirmed.

6. Fresh lymph node suspensions were prepared from seven patients in the acute phase of infectious mononucleosis (sterility tests on common substrates negative) and injected intracerebrally, intraperitoneally or subcutaneously into seven *Macacus* or *Cercopithecus* monkeys. In three cases, after about 19, 17 and 8 days respectively, there developed mild clinical symptoms with general enlargement of the lymph nodes, a slight increase in the mononuclear cells of the blood and in two of the cases a slight rise in rectal temperature. These changes could be reproduced in new monkeys by the inoculation of suspensions obtained from extirpated lymph nodes. In this way it appeared as if respectively five, two and three consecutive passages were obtained. The lymph nodes of the monkeys in question, when sectioned and stained or photo-

graphed unstained in ultraviolet light at 2570 Å showed the microscopic picture of an irregular, pleomorphic, mononuclear and large-celled hyperplasia, closely resembling that in the lymph nodes of human infectious mononucleosis. Sections from the lymph nodes of control monkeys showed no such alterations.

7. Heparinized blood or plasma from patients in the acute stage of infectious mononucleosis was transfused into five healthy medical students who volunteered for the purpose. One of these healthy subjects who had thus received 250 cc of heparinized blood developed after an incubation period of eighteen days a clinical, haematological, serological and histological disease picture indistinguishable from that of a typical case of infectious mononucleosis.

8. In sixteen cases of infectious mononucleosis, extirpated lymph nodes were examined microscopically. Sections from all of these lymph nodes revealed the picture of a pleomorphic, mononuclear and large-celled hyperplasia such as has been described by previous investigators. In three cases pieces of tonsillar tissue were excised and examined microscopically. Two cases revealed the noncharacteristic picture described by FOX while the third presented an appearance resembling that occurring in lymph nodes as described by FAHLÉN in one of his cases. Microphotographs of lymph node tissue were made in 12 cases at the nucleic-acid absorption maximum in ultraviolet light (at 2570 Å. E.) using CASPERSSON'S technique on the basis of the Köhler ultraviolet procedure. In three cases in immediate conjunction with the lymph node extirpation, smear preparations were made with as gentle technique as possible and it was these which offered the best opportunity for analysis of the finer cytological details. The microphotographs of preparations examined in this way showed identical pictures and revealed numerous large cells of varying diameter in addition to masses of lymphocytes. These large cells often exhibit a cytoplasm which absorbs ultraviolet peculiarly intensely (at 2570 Å) indicating the presence of large quantities of cytoplasmic nucleic acids. The cells in question usually show irregularities in the cytoplasm, as well as granular foci exhibiting intense ultraviolet absorption and surrounded by halo-like zones of only slight absorption. Sometimes there are similar punctate foci of only slight ultraviolet absorption surrounded by zones of intense absorption. The nuclear membranes usually seem to stand out prominently; the nucleoli are strikingly

large and irregular and generally surrounded by irregular zones of chromatin. These changes were not found in the control material and can only be interpreted as obviously pathological phenomena. The presence of a virus would explain their development. In any case in agreement with *CASTERSSON* they may be regarded as the cytochemical expression of a disturbance of the system of protein formation stimulated to great activity but not to mitosis.

In none of the sixteen lymph nodes extirpated during the acute phase of the disease was it possible to demonstrate any morphological structures diagnosable as microorganisms of bacterial or protozoal nature, either in smear preparations and sections stained according to current methods or in unstained sections on ultraviolet microphotography at the absorption maximum of nucleic acid.

9. The results of these investigations would seem to provide support for the assumption, previously based on clinical grounds, that human infectious mononucleosis is due to a virus with a specific lymphotropic affinity.

# CASE REPORTS

CASE 1. Serafimer Hospital Med. Clin. II 1239/1937. M. R. 21-years old railway employee. Previously always healthy. Gradual onset 14 days before admission with slight malaise and pain in the small of the back. A week after the first symptoms he noticed a rapidly increasing swelling on the left side of the neck. At the time his throat was swollen and there was pain on swallowing. His temperature rose to about 38° C.

*Status on admission* Oct. 10/37. Temperature 38.4° C. Fine prickly, clear red rash around the neck as well as over the shoulders and chest. On the left side of the neck above the sternocleidomastoid just behind and below the angle of the jaw is a lymph node mass about 8—10 cm in diameter, not discrete rather soft and slightly tender. On the right side of the neck as well as in each axilla are a number of similar swollen lymph nodes some as large as hazel nuts. There are none in the inguinal regions. There is swelling and intense redness of the throat and tonsils. The lower pole of the spleen is palpable.

*Laboratory data.* Blood: Hb 100 %, Rbc 4 800 000, Wbc 13 600, Polymorphonuclears 15 %, Mononuclears 85 % (large numbers of primitive mononuclears). Wassermann and Kahn negative. M.B.R. II negative. Sedimentation reaction 6 mm in 1 hr. Urine no abnormality. Hetero-agglutinin titer according to Paul & Bunnell (actual dilution) 1/1024. Direct smear and cultivation of tonsillar swab showed ordinary pharyngeal flora. Lymph node biopsy Oct. 15th: Definite large-celled reaction extending from the sinus areas into the lymphatic tissues which are reduced to small follicles with or without germinal centers. The large cells have loose, slightly basophilic cell bodies and large vesicular nuclei with one or more nucleoli. They show a certain amount of polymorphism. A small number of cells of the same type have 2 or 3 nuclei. Fairly numerous mitoses (Henschen). Aerobic and anaerobic cultures from the excised lymph nodes were still sterile on Oct. 29th. On the evening after the biopsy the temperature was 39.9° C. Blood culture taken then was still sterile 5 weeks later.

The patient left the hospital afebrile after 7 days. He still had 12 000 white blood cells of which 82 % were mononuclears and the hetero-agglutinin titer was 1/512.

CASE 2. Serafimer Hospital Med. Clin. II 120/1938. P.O.S. 21-years old medical student. Previously healthy. During the last days of December 1937 had had pain on swallowing and a swollen throat. As

the general feeling of malaise increased during the following days, he took to bed on January 2/1938.

*Status on admission* Jan. 10/38. Temperature 38.9° C. No exanthema. Behind and in front of both sternocleidomastoids are a number of freely movable, rather soft, slightly tender lymph nodes of the size of peas and beans. Each axilla and inguinal region contains a number of similar nodes up to the size of beans. The pharynx is deep red and swollen and the tonsils are coated. The right tonsil shows a small necrotic area. (Direct smear and culture of tonsillar swab showed ordinary pharyngeal flora.) The liver and spleen are not palpable. The internal organs are otherwise negative.

*Laboratory data.* Sedimentation reaction 20 mm in 1 hour. Urine no abnormality. Blood: Hb 96 %, Rbc 5 500 000, Wbc 10 200, Polymorphonuclears 26 %, Mononuclears 74 % (Profuse numbers of primitive mononuclears). Hetero-agglutinin titer according to Paul & Bunnell: Positive agglutination in 1/512, a trace in 1/1024 (final dilution). Wassermann and Kalin negative, M.B.R. II negative. Lymph node biopsy Jan. 8th: Hyperplastic lymph node with primary and secondary follicles. The sinus areas and also the lymphatic tissue show a definite increase in the macrophage elements. In the stroma and small blood vessels are small clumps of polymorphonuclear leucocytes. Hyperplastic lymphadenitis (Henschen). Aerobic and anaerobic cultures from the excised lymph nodes were still sterile on Feb. 3rd. Blood cultures taken Jan. 5th and 6th were still sterile after 5 weeks.

The patient left hospital after 7 days. He had no more subjective discomfort but the enlargement of the lymph nodes was still present. The white blood cell count was 7200 of which 65 % were mononuclears. The hetero-agglutinin titer according to Bunnell and Paul was still 1/512.

CASE 3. Serafimer Hospital Med. Clin. II 445/1938. B. M. N. 27-years old medical student. Previously healthy except for common colds. On March 30th he had noticed some swollen and tender lymph nodes submandibularly on the left side. During the following days there was increasing soreness of the throat. On April 1st there were still more swollen lymph nodes on the left side of the neck as well as for the first time a number of similar soft, slightly tender, freely movable lymph nodes on the right side of the neck. No malaise and no exanthema. Temperature 37.6° C.

*Status on admission* April 2/38. General condition good. Temperature 37.2° C. No exanthema. There is no conjunctivitis or oedema of the eyelids. The pharynx and tonsils are intensely reddened and slightly oedematous but otherwise without abnormality. Along the left sternocleidomastoid muscle are some 5—6 tender, soft, freely movable lymph nodes up to the size of hazel nuts. Along the right sternocleidomastoid are some similar nodes up to the size of beans. In the right axilla is a lymph node the size of a hazel nut and in both inguinal



regions some nodes the size of grains of rice. The internal organs are not abnormal on physical examination. The liver is not enlarged but the spleen is definitely so.

*Laboratory data:* Blood: Hb 100 %, Rbc 5 200 000, Wbc 12 800. Differential count: Neutrophils 32 %, Eosinophils 1 %, Mononuclears 67 % (Table 1, Page ). Hetero-agglutinin titer according to Bunnell & Paul 1/512 (final dilution, see also Table 1, Page ). Wassermann, Kahn and the M.B.R. II tests negative. Urine no abnormality. Blood culture still sterile on May 4th. At biopsy April 2nd a cervical lymph node was removed. Cultures still sterile on May 4th. Microscopy: General hyperplasia with the structure of the node diffusely obliterated and numerous lymphocytes and large light cells. In one circumscript area typical recent tuberculosis (Henschen).

The patient left the hospital after 5 days, afebrile but with still palpable lymph nodes.

CASE 4. Serafimer Hospital Med. Clin. II 1379/1938. E.W.H.A. 22-years old male employee. Previously healthy except for occasional infections in the upper respiratory passages. About a fortnight prior to admission he had not felt well and had complained of headache. A week later he developed a sore throat, pain on swallowing and swollen lymph nodes first on the right and then on the left side of the neck. Stayed in bed the last few days before admission because of rising temperature, chills and intense general malaise. For the last days was unable to swallow anything but fluids because of swollen throat and tonsils. No other symptoms.

*Status on admission* Oct. 12/1938. Temperature 39.3° C. No exanthema. Pharynx and tonsils reddened. Tonsils enlarged and showing necrotic foci. On each side of the neck behind and below the angle of the jaw is a lymphoma consisting of several soft slightly tender nodes up to the size of walnuts and plums, the entire mass being larger than an egg. In both axillae and inguinal regions are a number of similar lymph nodes up to the size of beans. The spleen is palpable. Otherwise the internal organs reveal no abnormality on physical examination.

*Laboratory data.* Blood: Hb 70 %, Rbc 4 200 000, Wbc. 12 300. Differential count: Neutrophils 30 %, Lymphocytes 70 % of which 25 % are pathological forms (Table 1). Hetero-agglutinin titer 1/512 (final dilution). Wassermann, Kahn and M.B.R. II tests negative. Sedimentation rate 8 mm/1 hr. Urine and faeces not abnormal. Blood culture from Oct. 12th still sterile on Nov. 20th. Biopsy Oct. 12th: Excision of a cervical lymph node the size of a walnut. Cultures still sterile on Oct. 20th. Microscopy: Hyperplasia with a certain obliteration of the architectural structure. The tissues between the follicles have a remarkable large-celled character and consist predominantly of cells with large rounded vesicular nuclei and one to two large prominent nucleoli. There are also lymphocytes and

plasma cells in smaller quantities. Mitoses are rather numerous (Henschen).

The patient left the hospital on Oct. 18th, afebrile but with a few still slightly enlarged lymph nodes.

CASE 5. St Erik's Hospital Med. Clin. IV 8235/1938. E. M. H. Female 23 years of age.

Orthostatic albuminuria since childhood. Tonsillectomy and appendectomy while still of school age. Otherwise always healthy. A history of ten days of intense general malaise and headache, sore throat and a temperature around 38° C. No other symptoms.

*Status on admission* Dec. 3rd 1938. General condition good. No exanthema. Pharynx reddened. Tonsils removed. Along both sternocleidomastoids are a considerable number of soft, slightly tender, freely movable lymph nodes, up to the size of hazel nuts. In each inguinal region are some 4 or 5 similar lymph nodes up to the size of peas. There are no enlarged nodes in the axillae. Roentgen examination shows some enlargement of the hilus shadows. The liver and spleen are not enlarged. Otherwise the internal organs show no abnormality.

*Laboratory data.* Blood: Hb 92 %, Rbc 4 600 000, Wbc 11 300. Differential count: Polymorphonuclears 13 %, Mononuclears 87 % with numerous pathological lymphocytes (Table 1). Hetero-agglutinin titer according to Bummell & Paul 1/2048 (final dilution). Wassermann, Kahn and M. B. R. II negative. Urine not abnormal. Blood culture from Dec. 7th still negative on Jan. 3rd. Biopsy for excision of cervical lymph node. Cultures negative on Dec. 27th. Microscopy: Some obliteration of the architectural structure and a pathological increase in the different mononuclear elements and macrophages (Henschen).

The patient left hospital on Dec. 18th, afebrile and subjectively well but with persistent slightly enlarged lymph nodes.

CASE 6. Sabbatsberg Hospital Med. Clin. II 956/1938. A. A. G. E. Male employee 24 years of age.

Previously healthy except for occasional attacks of paroxysmal tachycardia. Present illness began about 2 weeks ago with increasing malaise and rising temperature. Pain on swallowing as well as abdominal pain developed on the day before admission. Otherwise no symptoms.

*Status on admission* Dec. 8th 1938. General condition good. Temperature 38° C. No exanthema. Pharynx and tonsils reddened and swollen with necrotic foci in the latter. A couple of soft tender bean-sized lymph nodes below the angle of the jaw on each side of the neck. Spleen palpable. Otherwise the internal organs show no abnormality on physical examination.

*Laboratory data.* Blood: Hb 85 %, Rbc 4 400 000, Wbc 12 400.

Differential count: Segmented 5 %, Nonsegmented 30 %, Lymphocytes 66 %, with a high percentage of pathological cells, Monocytes 3 % (Table 1). Wassermann, Kahn and M. K. B. II negative. Sedimentation rate 13 mm/1 hr. Hetero-agglutinin titer according to Bunnell & Paul 1/4096 (final dilution). Urine not abnormal. Blood culture taken Dec. 13th still sterile on Feb. 2nd. Biopsy Dec. 16th with removal from the neck of a lymph node mass the size of a walnut. Cultures sterile. Microscopy: Lymph node tissues permeated by large clear cells with large clear nuclei with the chromatin in irregular granules and by fibroblastic cells as well as an occasional giant cell. No eosinophils or other evidence of Hodgkin's disease. Here and there are areas where the picture described above is less typical and the sinuses to which the chief changes are localized seem to be filled with cells forming collagenous connective tissue. The isolated mitoses are not of the type seen in malignancy. There is no evidence of tuberculosis or syphilis. The tissue shows a subacute non-specific reaction of the reticulo-endothelial system (WILTON).

The patient left hospital on Dec. 21st, afebrile and subjectively without symptoms but with some still slightly enlarged lymph nodes.

CASE 7. St. Erik's Hospital Med. Clin. IV 8467/1938. I.E.E.P. Woman factory worker 19 years of age.

Previously healthy. Acute onset Dec. 8th/1938 with intense general malaise, headache, pain in the lumbar region and an evening temperature of 38.5° C. The fever increased to 39.9° C during the following days. There was no cough or soreness of the throat.

*Status on admission* Dec. 13th 1938. General condition good. No exanthema. Tonsils reddened and enlarged without necrotic foci. Behind both angles of the jaw and along the sternocleidomastoids a number of slightly tender, soft, freely movable lymph nodes in size up to that of large beans. No enlargement of the nodes in the axillae or inguinal regions. No abnormality of the internal organs on physical examination. No enlargement of the spleen and liver. No abnormality of the lungs and heart on roentgen examination.

*Laboratory data.* Blood: Hb 100 %, Rbc 5 100 000, Wbc 5 800. Differential count: Segmented 6 %, Nonsegmented 23 %, Lymphocytes 56 %, Monocytes 15 %. Wassermann, M. B. R. II and M. K. R. II negative. Sedimentation rate 14 mm/1 hr (Table 1). Hetero-agglutinin titer according to Bunnell & Paul 1/2048 (actual dilution). Blood cultures on Dec. 14th (39.4° C) and 16th (38.4° C) still sterile on Jan. 6th. Biopsy Dec. 18th with removal of a lymph node. Microscopy: The lymph node structure in the peripheral regions is well retained and shows secondary follicles. In the central regions however the picture is dominated by large cells with light protoplasm and chromatin often in the form of granules. There is no evidence of malignancy, tuberculosis or Sternberg's disease. The picture is that of a non-specific reaction from the cells of the reticulo-

endothelial system (WILTON). Aerobic and anaerobic cultures from the excised node are still sterile on Jan. 6th.

The patient left the hospital on Jan. 20th, afebrile and with only 38.5 % mononuclear cells in the blood but still with palpable enlargement of the lymph nodes of the neck.

CASE 8. Sabbatsberg Hospital Otology Clin. 2151/1938. P. H. E. Male 24 years of age.

Previously always healthy. About one week before admission acute onset with a sore throat and pain on swallowing. Slight increasing fever. Otherwise no symptoms.

*Status on admission* Dec. 31st 1938. General condition good. No exanthema. The pharynx and tonsils are intensely reddened, the latter markedly enlarged and with necrotic foci. Along both sternocleidomastoids are a number of soft, freely movable lymph nodes about the size of hazel nuts. There is no abnormality of the internal organs on physical examination. The spleen and liver are not enlarged.

*Laboratory data.* Blood: Hb 95 %, Rbc 5 500 000, Wbc 11 400. Differential count: Neutrophils 30 %, Basophils 1 %, Lymphocytes 62 %, Monocytes 4 % (Table 1). Hetero-agglutinin titer according to Bunnell & Paul 1/512 (actual dilution). Blood cultures taken on Jan. 3rd (38.9° C) and 4th (37.7° C) still sterile on Feb. 8th. Urine not abnormal.

The patient left the hospital afebrile on Jan. 9th with slightly enlarged lymph nodes.

CASE 9. Sabbatsberg Hospital Otology Clin. 2152/1938. G. B. A. Male hospital employee 23 years of age.

Previously healthy. About one week before admission he was taken acutely ill with a feeling of soreness and swelling in the throat and pain on swallowing. The fever and throat trouble increased during the following days and a colleague suspecting a peritonsillitis sent the patient to the hospital.

*Status on admission* Dec. 31st 1938. Temperature 39.2° C. General condition good. The pharynx and tonsils are reddened. The tonsils are large, firm and coated, the left one being displaced medially. Anterior rhinoscopy shows the mucous membrane swollen and reddened, with no secretion. Along the sternocleidomastoids on both sides are a small number of soft, freely movable, slightly tender lymph nodes up to the size of small hazel nuts. The internal organs show no abnormality on physical examination. The spleen and liver are not enlarged. Urine not abnormal.

*Laboratory data.* Blood: Hb 70 %, Rbc 4 200 000, Wbc 18 100. Differential count: Neutrophils 27 %, Eosinophils 1 %, Lymphocytes 70 %, Monocytes 2 % (Table 1). Hetero-agglutinin titer according to Bunnell & Paul 1/1024 (final dilution). Blood cultures from Jan. 3rd (39.1° C) and Jan. 4th (38.2° C) still sterile on Feb. 8th.

After a temperature of  $40.3^{\circ}\text{C}$  on Jan. 2nd, there was a rapid lysis, and the patient left hospital for further convalescence at home on Jan. 9th, afebrile, with only small lymph nodes still remaining, and with a differential count showing 80 % mononuclears.

CASE 10. Military Hospital Med. Clin. 69/1938. S. E. A. Male 18 years of age.

Previously healthy. Since a fortnight before admission increasing general malaise, sore throat, pain on swallowing and a temperature about  $38^{\circ}\text{C}$ . Moderate bronchitis. Since the temperature showed an upward trend, he was sent to the hospital. Otherwise no symptoms.

*Status on admission* Jan. 12th 1939. General condition good. Temperature  $38.6^{\circ}\text{C}$ . No exanthema. The pharynx and tonsils are reddened, the latter swollen and showing a number of necrotic foci. Behind and below both angles of the jaw are some soft and tender lymph nodes the size of beans. Along the left sternocleidomastoid and in both inguinal regions are a number of similar lymph nodes of about the same size. The internal organs are otherwise without abnormality on physical examination. The spleen is not palpable.

*Laboratory data.* Blood: Hb 84 %, Rbc 4 840 000, Wbc 14 000. Differential count: Segmented 33.5 %, Nonsegmented 4.5 %, Basophils 0.5 %, Lymphocytes 61.5 % (Monocytoid pathological cells 21 %) (Table 1). Bunnell & Paul test 1/1024 (final dilution). Wassermann, Kahn, M. B. R. II negative. For sedimentation rate see Table 1. Urine not abnormal.

The patient left hospital on Jan. 26th, afebrile and without symptoms or palpable lymph nodes and a blood count showing only 31 % mononuclear cells.

CASE 11. Military Hospital Med. Clin. 77/1939. E. B. P. Male 25 years of age.

Pleurisy 1937. Frequent X-rays of the lungs since then without abnormality. Otherwise always healthy. On Jan. 12th 1939 acute onset with general malaise, sore throat and pain on swallowing, pain between the shoulders and fever.

*Status on admission* Jan. 14th 1939. Temperature  $37.5^{\circ}\text{C}$ . General condition good. No exanthema. The pharynx and tonsils are reddened, the latter considerably enlarged and showing necrotic foci. The internal organs are without abnormality on physical examination. X-rays of the lungs show no abnormality. The patient was regarded as a case of common tonsillitis, but as his fever continued to rise, reaching  $39.6^{\circ}\text{C}$  on Jan. 26th a blood count was performed and the true nature of his angina was revealed. A number of slightly tender, soft and freely movable lymph nodes up to the size of beans were then found along the sternocleidomastoid muscles on each side of the neck, as well as in both axillae and inguinal regions.

*Laboratory data.* Blood (Jan. 25th): Wbc 10 700. Differential count:

Segmented 13 %, Nonsegmented 1 %, Lymphocytes 70.5 %, Monocytes 15.5 %. Hetero-agglutinin titer according to Bunnell & Paul 1/512 (final dilution).

The patient left hospital on Feb. 6th, afebrile and without symptoms, but with slightly enlarged lymph nodes still persisting.

CASE 12. Serafimer Hospital Med. Clin. I 212/1939. L. E. Female 20 years of age. Previously always healthy. On Jan. 24th 1939 acute onset with severe headache, oedema of the eyelids and general malaise. After some days she noticed fever,  $38^{\circ}$ — $39.5^{\circ}$  C, and went to the ophthalmological clinic complaining of her swollen eyelids. Since only a moderate conjunctivitis was present and X-rays of the nasal cavities showed no abnormality she was sent to the medical clinic for further examination.

*Status on admission* Feb. 2nd 1939. General condition good. Temperature  $39.2^{\circ}$  C. No exanthema. There is considerable facial oedema, with special localization in the eyelids. There is moderate conjunctivitis. The pharynx and tonsils are reddened, the latter small and without necrotic foci. On both sides of the neck from the supraclavicular region along the sternocleidomastoid to behind the angle of the jaw are a large number of not too soft, tender, freely movable lymph nodes, ranging in size up to that of large beans. In each axilla and inguinal region are a couple of similar nodes. The liver and spleen are not enlarged. The internal organs are otherwise negative on physical examination.

*Laboratory data.* Blood: Hb 80 %, Rbc 4 200 000, Wbc 8000. Differential count: Neutrophils 20 %, Mononuclears 80 % (Pathological monocytoid cells and monocytes 49 %) (Table 1). Hetero-agglutinin titer according to Bunnell & Paul 1/4096 (final dilution). The Wassermann test showed slow hemolysis in two of the three extracts used. Kahn, M.B.R. II negative. Sedimentation rate 21 mm/1 hr. Urine not abnormal. Blood cultures from Feb. 2nd 4th were still sterile after 5 weeks (March 6th). Biopsy was not performed.

The patient left hospital Feb. 15th, afebrile, without symptoms but with slightly enlarged lymph nodes and a blood count still showing 86 % mononuclears. The Bunnell and Paul test was 1/4096.

CASE 13. Serafimer Hospital Med. Clin. II /1939: S. K. B. Male hospital employee 18 years of age.

With the exception of common colds and an otitis simplex had always been healthy prior to admission. For some time had had slight rhinitis and a cough without expectoration. On May 13th acute onset with sore throat, pain on swallowing and a temperature of  $38^{\circ}$  C. On May 15th he discovered tender lymph nodes on his neck. Otherwise no symptoms.

*Status on admission* May 19th 1939. General condition good. Temperature  $39^{\circ}$  C. No exanthema. The pharynx and tonsils are reddened the latter considerably enlarged and showing necrotic foci. On each

side of the neck, from the supraclavicular region to the angle of the jaw along the sternocleidomastoids are a number of soft, moderately tender lymph nodes up to the size of beans. Behind and below the angles of the jaw these form masses the size of an egg on the right side and that of a plum on the left. In both axillae and inguinal regions there are similar lymph nodes the size of beans. The spleen is palpable. The internal organs are otherwise without abnormality on physical examination.

*Laboratory data.* Blood: Hb 102 %, Rbc 5 500 000, Wbc 10 700. Differential count: Polynuclears 28 %, Mononuclears 72 % (monocytoid, pathological cells 39 %). Wassermann, Kahn and M. B. R. II negative. Hetero-agglutinin titer according to Bunnell & Paul 1/512 (actual dilution). Urine no abnormality. Blood culture from May 20th still sterile on June 20th. Biopsy May 22nd: Cervical lymph node excised. Cultures showed sparse growth of *B. Friedländer* in a number of substrates. Microscopy: Hyperplastic lymphadenitis, with diffuse large-celled hyperplasia within the sinus regions, and almost complete obliteration of the general structure of the node. (HENSCHEN).

The patient left hospital May 26th, afebrile, without symptoms but with slightly enlarged lymph nodes still persisting. For the blood picture see Table 1.

CASE 14. Military Hospital Med. Clin. 1874/1939. H. S. A. Medical student aged 24. Previously always healthy. On Sept. 23rd 1939 taken acutely ill with fever, general malaise and muscular pains. During the following days a temperature around 39° C, but no other symptoms.

*Status on admission* Sept. 27th. General condition good. Temperature 39.3° C. No exanthema. The pharynx and tonsils are reddened, the latter enlarged. There are no palpable lymph nodes. The spleen is not palpable. The internal organs are otherwise without abnormality on physical examination.

*Laboratory data.* Blood: Hb 90 %, Rbc 4 500 000, Wbc 4 700. Differential count: Polymorphonuclears 35 %, Mononuclears 65 % (pathological cells of the kind found in infectious mononucleosis are present). Wassermann, Kahn and M. B. R. II negative. Urine no abnormality. On Sept. 30th a number of soft, tender lymph nodes up to the size of small beans were palpable along the sternocleidomastoid muscle on both sides of the neck, and also in the axillae and inguinal regions. Hetero-agglutinin titer according to Bunnell & Paul 1/128. Blood Oct. 9th: Wbc 10,200, Polymorphonuclears 19 %, Mononuclears 81 % (large numbers of typical infectious mononucleosis cells). Hetero-agglutinin titer 1/512 (final dilution).

The patient left hospital Oct. 23rd, afebrile and without symptoms.

CASE 15. Sabbatsberg Hospital Otology Clin. 1642/1939. L. A. G. K. A male 24 years of age.

Had had a tonsillectomy in 1936 for recurrent peritonsillitis on the left side. Otherwise always healthy previously. For two weeks had had increasing general malaise accompanied in the last week by fever and pain on swallowing. Tenderness on both sides of the neck for the last few days.

*Status on admission* Oct. 10th 1939. General condition good. No exanthema. The pharynx is reddened and on the left there is slight oedema and a necrotic focus the size of a pea in the remnant of the left tonsil. There are slightly tender lymph nodes of moderate size along both sternocleidomastoids. The internal organs are otherwise normal on physical examination.

*Laboratory data.* Blood: Hb 76 %, Rbc 4 050 000, Wbc 16 400, Neutrophils 16 %, Lymphocytes 80 % (with numerous typical pathological cells), Monocytes 4 %. Hetero-agglutinin titer 1/2048 (final dilution; Table 1). Wassermann, Kahn and M. B. R. II tests negative. Urine no abnormality.

The patient left hospital Oct. 21st, afebrile but with persisting blood changes and slightly enlarged lymph nodes.

CASE 16. Stockholm Epidemic Hospital 4348/1939. M. L. L. A female aged 19.

Previously healthy. On Oct. 9th 1939 acute onset with sore throat and fever. The temperature varied between 39° and 39.5° C the following days. Diphtheria was suspected and she was sent to hospital Oct. 14th.

*Status on admission* Oct. 14th 1939. General condition good. No exanthema. Large intensely reddened tonsils with a membranous coating of dirty gray colour. Posterior to the angles of the jaw and along both sternocleidomastoids are a number of soft, slightly tender lymph nodes up to the size of hazel nuts. The internal organs otherwise reveal no abnormality. The spleen which was not palpable on admission could just be felt under the costal arch for a few days around 20/10.

*Laboratory data.* Blood: Hb 80 %, Rbc 4 500 000, Wbc 21 200. Differential count: Mononuclears 78 % (numerous typical pathological cells), Polymorphonuclears 22 %. Hetero-agglutinin titer according to Bunnell & Paul 1/1024 (final dilution). Sedimentation rate 8 mm/1 hr (Table 1). Wassermann, Kahn and M. B. R. II negative. Urine no abnormality.

The patient left the hospital on Oct. 26th, afebrile but with slightly enlarged lymph nodes and the mononucleosis of the blood still persisting.

CASE 17. Stockholm Epidemic Hospital 4392/1939. I. E. A young girl of 14.

On Oct. 14th acute onset with pain on swallowing and fever up to



40° C during the following days. As diphtheria was suspected she was sent to hospital on Oct. 18th.

*Status on admission.* General condition good. No exanthema. The tonsils are markedly enlarged with greyish-white membranes medially and necrotic foci. Along both sternocleidomastoids and behind the angles of the jaw are a number of slightly tender lymph nodes. The spleen is not palpable. The internal organs are otherwise without abnormality. — During the days following the lymph nodes increased in size, and on Oct. 19th there were masses the size of an egg on each side of the neck.

*Laboratory data.* Blood: Hb 80 %, Rbc 4 000 000, Wbc 15 000. Differential count: Polymorphonuclears 38 %, Mononuclears 62 % (roughly 50 % of these are typical pathological forms). Bunnell & Paul test 1/4096 (final dilution). Sedimentation rate 21 mm/1 hr (Table 1). Wassermann, Kahn and M. B. R. II negative. Urine no abnormality.

The patient left hospital on Oct. 26th, afebrile and with scarcely palpable lymph nodes.

CASE 18. Sabbatsberg Hospital Med. Clin. II 851/1938. A female aged 17.

Previously healthy except for common colds, varicellae, pertussis and morbilli. Since a fortnight prior to admission increasing headache, and the last three days a temperature up to 38.4° C and a tender lymph node on the left side of the neck. Right-sided hemihyperalgesia since the day before admission. Otherwise no symptoms.

*Status on admission* Nov. 11th 1939. General condition good. Temperature 38.9° C. No exanthema. There is general enlargement of the lymph nodes and behind the left angle of the jaw is one slightly tender node the size of a hazel nut. Otherwise no abnormality was discovered in the internal organs or neurologically.

*Laboratory data.* Blood: Hb 68 %, Rbc 3 700 000, Wbc 11 500. Differential count: Nonsegmented 7 %, Segmented 13 %, Eosinophils 1 %, Lymphocytes 79 % (almost exclusively pathological forms). Bunnell and Paul test 1/2048 (final dilution). Sedimentation rate 8 mm/1 hr (Table 1). Wassermann, Kahn and M. K. R. II negative. Urine no abnormality. Biopsy Nov. 15th with removal of a lymph node the size of a hazel nut from the left inguinal region. Sections of this lymph node show marked hyperplasia and a rather intense proliferation of the reticulo-endothelial elements in the lymph sinuses. These elements consist of large polygonal cells with very large nuclei strikingly poor in chromatin and in general provided with a small distinct nucleolus. The sections stained with Giemsa show a rather large number of basophilic mast cells. In preparations stained to demonstrate plasma cells the picture is dominated by masses of larger or smaller cells with reddish granular protoplasm and rather deeply stained rounded nuclei. In the smaller type of these cells is often ob-

served a Radkern arrangement of the chromatin but in the larger type such a structure cannot be demonstrated which makes it seem probable that they are monocytes. Only sparse numbers of secondary follicles are present and in these are seen occasional mitoses. Cells in mitosis are also to be found in several places in the lymphatic sinuses. In a number of blood and lymph vessels the lumen is packed almost exclusively with large and small mononuclear cells. Nowhere is there evidence of specific inflammation or of malignancy. The microscopic picture corresponds well with that in infectious mononucleosis (LINDGREN).

On Nov. 21st the spleen was palpable and a jaundice had developed (Meulengracht 1:18, van den Bergh positive, Takata 000232100).

The patient left hospital on Dec. 9th afebrile and non-jaundiced but with slightly enlarged lymph nodes and 59 % mononuclears still present in the blood.

CASE 19. Serafimer Hospital Med. Clin. I 1320/1939. B. G. R. A female aged 24.

Previously always healthy. On Nov. 20th taken acutely ill with general malaise, pain on swallowing and tenderness behind the angles of the jaw. During the following days increasing fever and oedema of the face, especially of the eyelids. Otherwise no symptoms.

*Status on admission* Nov. 28th 1939. General condition good. Temperature 38.6° C. No exanthema. Pronounced palpebral and periorbital oedema. The pharynx and tonsils are intensely reddened, the latter the size of walnuts with greyish-white membranes and several necrotic foci. Foetor ex ore. Behind and below the angles of the jaw on each side of the neck are a number of slightly tender lymph nodes, freely movable and in size up to that of hazel nuts. There are no lymph nodes in the axillae or inguinal regions. The spleen is palpable and slightly tender. The internal organs are otherwise without abnormality on physical examination.

*Laboratory data.* Blood: Hb 85 %, Rbc 4 600 000, Wbc 11 000. Differential count: Polymorphonuclears 30 %, Mononuclears 70 % (most of which are pathological lymphocytes of characteristic shape). Binnell & Paul test 1/256 (final dilution). Blood cultures still sterile on Dec. 22nd. Sedimentation rate 17 mm/1 hr. Wassermann, Kahn, M. B. R. II negative. Urine no abnormality.

The patient left hospital Dec. 29th for further care at home.

CASE 20. Serafimer Hospital Med. Clin. II 1327/1939. K. F. A. A male aged 23.

Previously always healthy. Gradual onset on Nov. 22nd and 23rd with increasing general malaise, headache, sore throat and pain on swallowing so that he took to bed. During the following days he became feverish and developed enlarged cervical lymph nodes which became increasingly tender. Otherwise no symptoms.

*Status on admission* Nov. 29th 1939. General condition good. Temperature 38.6° C. No oedema. No exanthema. The pharynx and tonsils are reddened, the latter enlarged and showing necrotic foci. Behind and below the angles of the jaw on each side is a mass the size of an egg, composed of a number of soft, freely movable, slightly tender lymph nodes. In both axillae and inguinal regions are a number of similar lymph nodes up to the size of beans. The spleen is not palpable. The internal organs are otherwise without abnormality.

*Laboratory data.* Blood: Hb 90 %, Rbc 4 600 000, Wbc 9 500. Differential count: Polymorphonuclears 36 %, Mononuclears 64 % (numerous pathological cells). Hetero-agglutinin titer according to Bunnell & Paul 1/4096 (final dilution). Sedimentation rate 31 mm/1 hr (Table 1). Wassermann, Kahn, M. B. R. II negative. Urine no abnormality. Blood culture from Nov. 27th still sterile on Dec. 22nd. Excision on Nov. 30th of two cervical lymph nodes the size of beans. Microscopic examination: The general structure of the nodes seems diffusely obliterated. Within large areas there is a pronounced large-celled reaction apparently arising from the sinus endothelium. There is an occasional giant cell (HENSCHEN). Aerobic and anaerobic cultures from the nodes were negative on Dec. 10th.

The patient left the hospital on Dec. 6th afebrile.

CASE 21. Sabbatsberg Hospital Otology Clin. 2038/1939. S. T. H. A male aged 17.

Previously healthy. On Dec. 23rd onset with acute general malaise, sore throat, chills and rising fever. Temperature about 39° C during the following days. Otherwise no symptoms.

*Status on admission* Dec. 27th 1939. General condition good. Temperature 39.1° C. No exanthema. The tonsils are swollen and reddened, with large necrotic foci. There are tender lymph nodes the size of large beans behind the angles of the jaw and similar tender lymph nodes in the axillae and inguinal regions. The spleen is palpable. The internal organs are otherwise without abnormality on physical examination.

*Laboratory data.* Blood: Hb 79 %, Rbc 4 100 000, Wbc 12 000. Differential count: Polymorphonuclears 11 %, Mononuclears 89 % (numerous pathological cells). Bunnell & Paul test 1/256, on Dec. 31st 1/1024 (final dilution). Urine no abnormality. Blood culture still sterile on Jan. 31st. Biopsy Dec. 29th with excision of lymph node from right inguinal region. Microscopy: The lymph node shows the picture of a relatively moderate hyperplasia and proliferation of reticulo-endothelial elements, especially in the sinus areas of the lymph node. In addition to lymphocytes and plasma cells there are profuse number of large mononuclear cells with nuclei very poor in chromatin and one or occasionally two distinct nucleoli. Moderate numbers of basophilic mast cells are especially to be seen in the Giemsa stained tissue. The most pronounced picture is obtained in the sections stained to demonstrate plasma cells

where both the plasma cells just described as well as the large mononuclear elements stand out clearly due to the red staining of the cytoplasm. Careful study under the oil immersion lens shows that a large number of the large mononuclear cells are in mitosis. The histological picture corresponds well with that characteristic of infectious mononucleosis. There is no evidence of specific inflammation or of malignancy (LINDGREN).

The patient left the hospital Jan. 2nd afebrile but with slight persistent enlargement of the lymph nodes and with abnormal changes in the blood.

CASE 22. Karolinska Hospital Med. Clin. 1304/1940. K. H. A. H. A male aged 23.

Always healthy previously except for common colds. Onset four or five days before admission with general malaise, chills and rising fever. Could swallow only fluids the last two days. Otherwise no symptoms.

*Status on admission* Oct. 3rd 1940. General condition good. Temperature 39.1° C. No exanthema. The pharynx and tonsils are intensely inflamed, the latter showing several necrotic foci and considerable peritonsillar oedema. In the supraclavicular fossa, along the sternocleidomastoid, and behind the angle of the jaw on each side there is a lymph node mass consisting of a considerable number of soft, slightly tender, freely movable lymph nodes up to the size of walnuts. In both inguinal regions and axillae are a number of similar lymph nodes, in size up to that of beans. The spleen was not palpable on admission but could perhaps be palpated on Oct. 8th. The internal organs are otherwise without abnormality on physical examination. The X-rays of the lungs show no abnormality.

*Laboratory data.* Blood: Hb 84 %, Rbc 4 100 000, Wbc 17 800. Differential count: Segmented 17.5 %, Nonsegmented 5 %, Basophils 0.5 %, Mononuclears 77 % (with numerous typical pathological cells). Bunnell & Paul tests gave on Oct. 3rd no agglutination, on Oct. 6th 1/512 and on Oct. 9th 1/1024 (final dilution; Table 1). Sedimentation rate 12 mm/1 hr. Wassermann, Kahn and M. B. R. II negative. Urine no abnormality. Blood cultures made on Oct. 4th and 5th were still sterile on Nov. 11th. Biopsy: On Oct. 5th a lymph node was excised from the neck of the patient. Microscopy: The architectural structure of the lymph node is almost completely obliterated. The areas between the vestiges of the follicles are occupied by tissue composed chiefly of large clear cells but between which can be distinguished lymphocytes and larger cells with nuclei poor in chromatin as well as rather large epithelioid elements in profusion. There are occasional mitoses. There are a few eosinophils. The picture corresponds to that seen in infectious mononucleosis (HENSCHEN). Aerobic and anaerobic cultures from the excised lymph nodes were still sterile on Nov. 5th.

The patient left hospital on Oct. 16th, afebrile but with slightly

enlarged lymph nodes still present as well as the blood picture of infectious mononucleosis.

CASE 23. Karolinska Hospital Med. Clin. 319/1941. A female 31 years of age.

Previously healthy. Onset on Feb. 12th with conjunctivitis, oedema of the eyelids and an evening temperature of 38.8° C. During the following days greater palpebral oedema, headache and increasing general malaise. From Feb. 16th tender cervical lymph nodes and from Feb. 18th a sore throat with intense pain on swallowing.

*Status on admission* Feb. 21st 1941. General condition good. Temperature 38.8° C. No exanthema. There is a moderate injection of the conjunctivae but heavy oedema of both eyelids. The pharynx and tonsils are intensely swollen and reddened, the latter showing several necrotic foci. Behind and below the angle of the jaw on both sides are three to four soft, slightly tender, freely movable lymph nodes ranging in size up to that of a hazel nut. Along both sternocleidomastoids in the axillae and in the inguinal regions are a number of similar swollen lymph nodes about the size of beans. The internal organs show no abnormality. The spleen is not palpable.

*Laboratory data.* The urine is not abnormal. The Wassermann, Kahn and M. B. R. II tests are negative. The blood counts may be read off in the following table.

Date	Hb %	Rbc	Wbc	Polymorphonuclears				Monocytes %	Lympho- cytes <sup>1</sup> %	Plasma cells %	Sed. Rate mm/1 hr	Bunnet & Paul test Final dil.
				Neutr.		Eos. %	Bas. %					
				Non- segm. %	Segm. %							
18/2	83	4 290 000	10 900	6	22	1	—	6	64	1	—	1 : 64
20/2			18 400	7	20	—	—	2	71	—	—	
22/2	81	4 140 000	14 100	4	18	0.5	0.5	1.5	75	0.5	21	1 : 128
26/2			11 000	2	10	1	—	4	83	—	34	
5/3	89	4 650 000	6 800	3	16	—	—	4	77	—	14	3/3, 1 : 128

<sup>1</sup> Numerous typical pathological cells in all smears.

Blood cultures taken on Feb. 22nd and 25th were still sterile on March 26th. At biopsy Feb. 22nd a cervical lymph node the size of a bean was removed. Microscopy: The sections seem oedematous and the general structure of the tissue is diffusely obliterated. There is polymorphous interfollicular hyperplasia with great numbers of large light cells with large vesicular nuclei and with innumerable plasma cells. In the sinuses are lymphocytes, plasma cells and a small number of large histiocytes (HENSCHEN). Microphotograph in ultraviolet light Fig. 16. On Feb. 26th the spleen was palpable and the lymph nodes

were as before. The tonsils had improved and the necrotic foci were gone. On March 4th the spleen was no longer palpable, there was no palpebral oedema and the lymph nodes were decreasing in size. On March 9th the patient was symptom-free but slightly enlarged lymph nodes and the blood count of infectious mononucleosis were still present.

CASE 24. Karolinska Hospital Med. Clin. 1577/1941. G. O. S. A male student 19 years of age.

Previously healthy. On Sept. 23rd 1941 the patient noticed slightly tender lymph nodes on left side of the neck. During the following days there was increasing general malaise and headache. On Sept. 29th the temperature was  $39.4^{\circ}\text{C}$ , the lymph nodes on the left had enlarged and new ones appeared on the right side of the neck. There was also abdominal pain.

*Status on admission* Sept. 30th. Temperature  $38.6^{\circ}\text{C}$ . No exanthema. The pharynx and tonsils are intensely reddened, the latter with a number of necrotic foci. On each side of the neck along the sternocleidomastoids are a number of slightly tender lymph nodes up to the size of hazel nuts. They form an egg-sized mass on the left side. The preauricular and submandibular lymph nodes are the size of peas. In both axillae and in the inguinal regions are similar, slightly tender, soft, bean-sized lymph nodes. The heart and lungs show no abnormality on physical or roentgen examination. The spleen is palpable and roentgen examination reveals considerable enlargement ( $11 \times 22$  cm.). The liver is not enlarged.

*Laboratory data.* Blood: Hb 100 %, Rbc 5 600 000, Wbc 10 000. Differential count: Nonsegmented 5 %, Segmented 21 %, Eosinophils 1 %, Lymphocytes 70 %, Monocytes 3 % (Table 1, Page ). The Wassermann, Kahn, M. B. R. II and M. K. R. II tests were negative. The sedimentation rate and the results of the Bunnell & Paul tests are given in Table 1. The blood culture taken on Oct. 3rd when the patient had a rectal temperature of  $40^{\circ}\text{C}$  was still sterile on Oct 31st.

On Oct. 6th the temperature was  $37.4^{\circ}\text{C}$ . At biopsy a cervical lymph node the size of a hazel nut was removed. Microscopy: Sections show a very hyperplastic lymph node with obliteration of most of the architectural structure. There is hyperplasia of cells of a large clear type. The secondary follicles are often distinct. Microscopic examination of a piece of the right tonsil shows a hyperplastic tonsillitis. The picture in the lymph node as well as the tonsil corresponds to that seen in infectious mononucleosis (HENSCHEN). Microphotographs in ultraviolet light Fig. 18—21. Aerobic and anaerobic cultures from the above-mentioned lymph node were sterile on all substrates with the exception of one broth in which staphylococcus albus was found.

On Oct. 17th the patient was discharged afebrile with considerable decrease in the size of the lymph nodes and spleen.

CASE 25. Karolinska Hospital Otology Clin. 2024/1941. K. O. P. A male aged 23.

Previously healthy. About 2 weeks before admission acute onset with fever and pain on swallowing. Tender cervical lymph nodes the last week. Otherwise no symptoms.

*Status on admission* Oct. 5th 1941. General condition good. Temperature 40.2° C. No exanthema. The pharynx and tonsils are inflamed, the latter considerably enlarged and with several necrotic foci. Along the sternocleidomastoids on each side of the neck are a number of lymph nodes the size of beans. The spleen is not palpable. The internal organs are otherwise without abnormality.

*Laboratory data.* Blood: Hb 100 %, Rbc 5 000 000, Wbc 11.000. Differential count: Nonsegmented 5.5 %, Segmented 34.5 %, Lymphocytes 54.5 % (pathological lymphocytes about 21 %), Monocytes 5.5 % (Table 1). Bunnell & Paul test 1/1024 (final dilution). Urine no abnormality. Blood culture taken Oct. 7th still sterile on Nov. 11th. A small piece of tissue was excised from the tonsils on Oct. 8th Microscopy: The mucous membrane shows a definite, in some places very dense infiltration with inflammatory cells of different types, chiefly lymphocytes. There are isolated plasma cells and eosinophils as well as a few histiocytes. There is a small defect in the surface epithelium. There is a small crust over the defect and leucocytes are very numerous beneath it. There is nothing pathognomonic of infectious mononucleosis (HENSCHEN).

The patient left the hospital on Oct. 13th, afebrile, but with slightly enlarged lymph nodes and a blood picture with 81.5 % mononuclears.

CASE 26. Karolinska Hospital Med. Clin. 2050/1941. P. E. W. A surveyor 28 years of age.

Previously always healthy. Onset during the first two weeks of December 1941 with increasing general malaise. He played tennis as usual up to Dec. 18th when he felt in bad condition during his game. On Dec. 20th when he went to bed his temperature was 38.7° C in the morning and 39.4° C in the evening and he had a number of slightly tender lymph nodes on the right side of his neck. His temperature varied the following days between 38.5° and 39.5° C. His sister a physician referred him to the writer on Dec. 24th.

*Status.* Dec. 24th 1941. No exanthema. The pharynx and tonsils show no abnormality. Supraclavicularly and along the sternocleidomastoid on the right side of the neck are about a dozen slightly tender, soft lymph nodes ranging in size up to that of good-sized beans. There are a number of similar lymph nodes in both axillae and inguinal regions. The spleen is not palpable.

*Laboratory data.* Blood: Hb 114 %, Rbc 5 720 000, Wbc 18 000. Differential count: Segmented 11 %, Nonsegmented 4 %, Eosinophils 2 %, Lymphocytes 74 % (23 % pathological forms), Monocytes 9 %.

Hetero-agglutinin titer 1/4096 (final dilution). Blood culture still sterile on Jan. 30th (growth of rods and cocci in single broth). The patient was ordered to remain in bed at home but when in the following days he began to have a sore throat with increasing pain on swallowing, a rising temperature and on Dec. 27th 25 900 Wbc, he was admitted to hospital the next day.

*Status on admission.* Dec. 28th. General condition good. No exanthema. There is moderate enlargement of the tonsils which show no necrotic foci. The tonsils and pharynx are reddened. Supraclavicularly and along the sternocleidomastoids on both sides there are about a dozen soft slightly tender lymph nodes. On the right side they are up to bean size and on the left to peas. A number of similar lymph nodes are also to be found in each axilla and inguinal region. The spleen is palpable. Otherwise the internal organs show no abnormality.

*Laboratory data.* Blood: Hb 110 %, Rbc 5 800 000, Wbc 15 700. Differential count: Segmented 7 %, Nonsegmented 11 %, Lymphocytes 76.5 % (68 % pathological forms), Monocytes 5.5 % (Table 1). Bunnell & Paul test 1/4096. Wassermann, Kahn, M. B. R. II and M. K. R. II negative. Urine no abnormality. Sedimentation rate 15 mm/1 hr. Blood culture taken Dec. 29th sparse growth of diphtheroids in a couple of substrates. At biopsy dec. 29th a mass consisting of some five or six lymph nodes up to the size of hazel nuts was removed from behind the right sternocleidomastoid. The result of aerobic and anaerobic cultures was the growth of staphylococcus albus and diphtheroids in one single broth. Microscopy: The tissues show hyperplastic lymphadenitis. The interfollicular tissues are particularly hyperplastic showing large quantities of epithelioid cells, lymphocytes and plasma cells. There are few neutrophils and almost no eosinophils. The picture suggests infectious mononucleosis (HEN-SCHEN). Microphotographs in ultraviolet light Fig. 22.

The patient left hospital Jan. 3rd 1942, afebrile and without subjective discomfort but with slightly enlarged lymph nodes still present. The spleen was no longer palpable. Blood: Wbc 9 000. Differential count: Segmented 28 %, Nonsegmented 2.5 %, Eosinophils 3 %, Lymphocytes 65 % (pathological forms 29.5 %), Monocytes 0.5 %. Hetero-agglutinin titer 1/1024.

CASE 27. Karolinska Hospital Med. Clin. 2074/1941. I. E. H. A school girl 13 years of age.

Always healthy except for common colds. Acute onset Dec. 18th 1941 with fever, general malaise increasing palpebral oedema and pain on swallowing. On Dec. 27th she first noticed a number of small tender lymph nodes along the sternocleidomastoids.

*Status on admission.* Dec. 30th. General condition good. No exanthema. The conjunctivae are inflamed and there is marked oedema of the eyelids. The pharynx and tonsils are intensely reddened, the latter



considerably enlarged and with a number of necrotic foci. On each side of the neck along the sternocleidomastoids are some 10 to 12 soft, not tender lymph nodes up to the size of large beans. Both inguinal regions and the axillae contain some 2 or 3 similar lymph nodes. The spleen is not palpable. The internal organs are otherwise without abnormality.

*Laboratory data.* Blood: Hb 60 %, Rbc 4,500,000, Wbc 11,300. Differential count: Segmented 15 %, Nonsegmented 5 %, Eosinophils 0.5 %, Lymphocytes 78 % (pathological forms 61.5 %), Monocytes 1 %, Plasma cells 0.5 %. Hetero-agglutinin titer according to Bunnell & Paul 1/1024 (final dilution; Table 1). Sedimentation rate 14 mm/1 hr. Wassermann, Kahn, M.B.R. II and M.K.R. II tests negative. Urine not abnormal. Blood cultures from Dec. 31st and Jan. 2nd still sterile on Feb. 10th. At biopsy Jan. 2nd were removed some lymph nodes the size of peas from the left supraclavicular fossa. Aerobic and anaerobic cultures were still sterile on Jan. 25th (some sparse diphtheroid colonies on one aerobic blood agar plate were most certainly contamination). No microscopic examination was made. Microphotographs in ultraviolet light Fig. 23—25.

The patient left the hospital on Jan. 8th 1942, afebrile and without subjective discomfort but with slightly enlarged lymph nodes still present.

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## THE MECHANISM OF BLOOD SEDIMENTATION

BY

*JØRGEN E. THYGESEN*

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EJNAR MUNKSGAARD · COPENHAGEN 1942

# ACTA MEDICA SCANDINAVICA

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THE MECHANISM OF  
BLOOD SEDIMENTATION





# THE MECHANISM OF BLOOD SEDIMENTATION

BY

*JØRGEN E. THYGESEN*



*FINSEN LABORATORY*

---

EJNAR MUNKSGAARD  
COPENHAGEN 1942

Denne Afhandling er af det lægevidenskabelige Fakultet antaget til offentligt at forsvares for den medicinske Doktorgrad.

*København, den 16. December 1941.*

E. DAHL-IVERSEN

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## PREFACE

The present work was carried out in the Finsen Laboratory, Copenhagen. I wish to express my most sincere thanks to the director of the laboratory, *O. M. Henriques*, D. Sc., for placing the laboratory facilities at my disposal, for numerous stimulating discussions, and for the great interest he has taken in this work.

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The cinematographic studies of "rouleaux formation" were performed at the Biological Institute of the Carlsberg Foundation. My best thanks are due to the chief of this institute, *A. Fischer*, M. D., for his hospitality and his kind interest in my work.

In the theoretico-physical treatment of the orientation effect and of *Smoluchowski's* coagulation theory, *C. Møller*, Ph. D., has given his valuable advice for which I express my sincere thanks.

Some years ago, Professor *N. Bjerrum*, Ph. D., the Chemical Laboratory of the Royal Veterinary and Agricultural College, gave valuable instruction concerning electrolyte theory and electrolyte experiment. I take the opportunity to express my gratitude for this tuition without which I hardly would have been able to carry out the present investigations.

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Copenhagen, May 1942.

*J. E. Thygesen.*



## INTRODUCTION

The "blood sinking reaction" or "blood sedimentation test" which is of greatest significance for practical and theoretical medicine may best be characterized as a simple sedimentation experiment with an aggregating suspension. After addition of a substance inhibiting coagulation and careful mixing, the blood is sucked up into a vertically placed glass tube, and the thickness of the plasma layer above the sediment of the corpuscles is observed at a given moment.

The present thesis deals with the mechanism of the sinking reaction, especially with erythrocyte aggregation. The relation of this reaction to various physiological and pathological states, however, is disregarded.

In the treatment of biological problems, a frequently chosen way out is the *purely* experimental method. As a rule, the task of the practitioner is ended with the production of the respective phenomena under a number of different experimental conditions and a detailed description of his observations. In the field of biological research, the productiveness of an exchange between experiment and theory — characterizing pure physics — is not yet satisfactorily discerned. With the questions "why" or "how" the investigations approach the field of theory with its, for the moment, more or less realizable possibilities of checking. The scientific theory is always directly or indirectly based upon certain experimental facts, endeavouring to search for new remedies of rational mathematical investigations on the basis of already known natural laws. The practitioner's lack of interest in theoretical problems often originates from a wanting in scientific imagination and an insufficient understanding of mathematical symbols. The theory only enables us to decide whether "ideal" experimental conditions were chosen, and the theory turns our attention towards new experimental possibilities.



ities. In contrast herewith, the empirist is working blindly, since innumerable possibilities must be tried instead of a few well-weighed combinations which arise from a reasonable working hypothesis.

Since a complete experimental and theoretical study of the "blood sinking reaction" cannot be carried out by one investigator within a reasonable time, the author decided to elucidate the problem by theoretical considerations and orientating experiments. Because of this dualism between experiment and theory the presentation may appear diffuse and circumstantial. With respect to a reader interested in natural science who is not confident with biological problems, it is necessary to describe parts of the literature on "blood sedimentation" in general, a description which certainly appears trivial to the biologist. On the other hand, the biologist claims a somewhat popularized description of the theoretical treatment of the problems which, therefore, may seem rather trivial from the view of a mathematician.

As indicated in the respective sections, the results of some of the theoretical investigations have been published previously as preliminary works to the present thesis.

Among the results of the present investigation the most important point may be emphasized. It has been possible for the first time to give a mathematico-physical description of the forces which give rise to the conglomeration of the red blood corpuscles, viz. their so-called "rouleaux formation."

Presenting this book to the reader, it is therefore tempting to cite *Newton* whose thoughts completely represent our view of the world on macro- and microsystems "*Many things move me to suspect that everything (natural as well as mechanical) depends upon certain forces, in virtue of which the particles of bodies, through forces not yet understood, are either impelled together . . . , or are repelled and recede from one another*".

## Section I.

# THE PRINCIPLE OF BLOOD SEDIMENTATION.

### § 1. CHARACTERISTIC FEATURES FROM THE HISTORY OF BLOOD SEDIMENTATION.

A detailed review of the history of the blood sedimentation phenomenon is superfluous, since *R. Fåhræus* gave a masterly description of these phenomena in 1921 (109). The author will therefore confine himself to a few particularly characteristic features.

The tendency of the erythrocytes to cluster together with their flat sides against each other was already known to the most ancient investigators (*De Senac*, 1749 (377), *Della Torre*, 1776 (417), *W. Hewson*, 1777 (198), *E. Home*, 1818 (202)). *Hewson* compared the erythrocytes with piles of coins "... red particles of blood .... with their sides parallel like a number of coins". Already in the early literature, the pronounced aggregation of the erythrocytes in pathological blood is described. *John Hunter* (207), for example, mentions this phenomenon in his lectures, 1786, as follows: "In all inflammatory dispositions in the solids, whether universal or local, the blood has an increased disposition to separate into its component parts, the red globules become less uniformly diffused, and their attraction to one another becomes stronger, so that the blood, when out of the vessels, soon becomes cloudy and muddy and dusky in its colour, and when spread over any surface it appears mottled, the red blood attracting itself and forming spots of red".

From the illustrious monography "Das Blut", 1836, by the German haematologist *Hermann Nasse* (293) it is also apparent that the most important features in the blood sedimentation, viz. the aggregation of the corpuscles, was a well-known phenomenon. *Loc. cit.* p. 34 reads as follows: "Um das von *Schroeder van der Kolk* (1820) beschriebene Phänomen der Flockenbildung

wahrzunehmen, bedarf es keineswegs eines Mikroskops. Schon mit blossen Augen bemerkt man, wie dies auch der genannte Beobachter erwähnt, dass überall, wo wegen Entzündung die Ader geöffnet wird, an den Streifen, welche von den Rändern des auffangenden Gefässes abfliessendes Blut, selbst wenn es auch gar nicht faserhäutig ist, zurück lässt, Flocken oder kleine rote Punkte entstehen, die durch klare Lymphe von einander getrennt sind". The most important result of *Nasse's* investigations was his theory on blood sedimentation (*loc. cit.*, p. 236): "Bei der mikroskopischen Untersuchung des Blutes hatte ich gefunden, dass die Körnchen, je mehr sich ihrer verbinden, desto schneller zu Boden sinken und dass ganz besonders in dem faserhäutigen Blute die Neigung sich zu vereinigen auffallend gross ist, sowohl in dem frischen als in dem geschlagenen". *Nasse* (*loc. cit.*, p. 220), as earlier *Hewson*, clearly understood that the sedimentation phenomenon and the differences in the specific gravity of corpuscles and plasma do not stand in any close relation. Furthermore, he investigated the retarding influence of salts and the promoting influence of gum arabic on the aggregation of the corpuscles (*loc. cit.*, p. 231). In the wonderfully detailed description of the problem of blood sinking given by *Nasse* we find, moreover, some observations on the effect of shaking (*loc. cit.*, p. 86) and temperature fluctuations (*loc. cit.*, p. 212) on the sedimentation velocity.

At a later period, *F. Henle*, 1841 (187), and *Jones*, 1843 (214), discovered the parallelism between sedimentation velocity and aggregation, and in 1845, *Gulliver* (164) pointed out that the rapid sinking of horse blood is due to a physiological, very pronounced aggregation of the corpuscles. *Gulliver* noticed, furthermore, that the corpuscles of fresh or newly shaken blood sediment much more slowly in the beginning than later, in accordance with the fact that the aggregation takes a certain time to occur. The Danish physiologist *P. L. Panum*, 1851 (323), who was keenly interested in the study of blood, discovered (in analogy to *Nasse*) the influence of rouleaux formation (piles of coins) on the sinking velocity and the thickness of the buffy coat. He rejected *Henle's* stickiness theory of the aggregation and emphasized the advancing influence of fibrin on the aggregation. Apart from the agglomeration, a decrease in the number of erythrocytes causes a more rapid sedimentation and a thicker

crusta (if the coagulation of the blood does not occur too rapidly) so that repeated bleedings cause an increasing instead of a decreasing crusta.

*J. Dogiel*, 1879 (83), revealed that the normal aggregation phenomenon was extremely pronounced in the blood of a patient suffering from pneumonia. *Ph. Eisenberg*, 1903 (100), noticed a marked conglomeration of the red cells in a case of pyocyanous infection. *E. Biernacki*, 1894 (33), found, as already shown by *Hewson*, a less pronounced rate of sedimentation of defibrinated than of non-defibrinated blood. In 1897 (34), the same author published a work titled "Die spontane Blutsedimentierung als eine wissenschaftliche und praktisch-klinische Untersuchungsmethode" describing a method of investigation of the blood sinking in a number of diseases. *Biernacki* found the relation between the content of fibrin and blood sinking. In most of the diseases investigated the sinking velocity was increased. *O. Müller*, 1898 (292), applied a technique similar to that used by *Biernacki*. *H. Brat*, 1905 (46), investigated the effect of an addition of sodium chloride, gelatin or gum arabic on the blood sedimentation test of various animals. *A. W. Sellards*, 1908 (376), studied the effect of serum inactivated by heat on the rouleaux formation. *L. Berczeller* and *E. Stanker*, 1917 (25), reported the change of the rate of sedimentation after heating the blood (horse, sheep, and pig) to different temperatures. *J. de Haan*, 1918 (169), showed that the rapid sinking velocity of horse blood is caused by an intense rouleaux formation and that this rapid sinking can be annulled by adding a physiological sodium chloride solution.

The few publications in the period between 1850 and 1918 indicate a decreasing interest in the problem of blood sedimentation, and with the prosperity of cellular pathology these works, just as the earlier ones, fall into oblivion. Also *L. Hirschfeld's* demonstration of increased sinking speed in malaria, 1917 (201), is forgotten in spite of his prophecy of the importance of blood sinking as a method of clinical research. Not before *R. Fåhræus'* communication of a new pregnancy reaction, 1918 (107, 108), and the publication of all his results, 1921 (109), was the sedimentation test revived to a completely unexpected extent.

Since most of the very extensive literature on blood sediment-

ation deals with the reaction of blood sinking in physiological and pathological states, we may confine ourselves to referring to the valuable reviews by *R. Fåhræus*, 1921 (109) and 1929 (110), *A. Westergren*, 1924 (436), *G. Katz* and *M. Leffkowitz*, 1928 (221), *R. Höber*, 1928 (205), *M. Leffkowitz*, 1932 (249) and 1933 (250), and *H. Reichel*, 1936 (351). In the following, almost exclusively such publications will be cited which deal with the physico-chemical conditions of "rouleaux formation."

## § 2. DEFINITION OF THE PHENOMENON "ROULEAUX FORMATION".

Since the clustering together of the red blood corpuscles, the so-called haemagglutination, appears in different ways, the individual aggregation process can only be defined if it is produced under well-known experimental conditions. It is thus necessary for a definition of the "rouleaux formation" to describe the principles of the various types of haemagglutination.

We differentiate between normal agglutination and immune-agglutination.

Normal agglutination is found to occur partly as an agglutination of blood corpuscles from one species in the serum of another species — heterologous agglutination —, partly as an agglutination of blood corpuscles from one individual in the serum of another individual of the same species — homologous agglutination or iso-agglutination — and, finally, as an agglutination of an individual's corpuscles in the serum of the same individual — auto-agglutination.

Immune-agglutination appears in the serum of an animal after parenteral treatment with blood corpuscles of another animal whose corpuscles were introduced.

Iso-agglutination is caused by a specific antibody — agglutinin anti-A or anti-B bound to the corpuscles which are provided with receptors A and B, respectively — and may be described by a number of characteristics. The aggregation is completely irregular, the corpuscles clustering quite arbitrarily together, in contradistinction to the cylindrical conglomerates of rouleaux formation. The reaction is furthermore type-specific, *i. e.* iso-

agglutinin anti-A and anti-B do not affect the erythrocytes of the same individual or the same group.

The agglutinating serum loses its ability to agglutinate when coming into contact with homologous erythrocytes. The adsorbed agglutinin can be split off again by heating. Shaking or centrifuging increases the aggregation velocity. Shaking does not annul an agglutination which has already occurred, but produces at the most a slight reduction of the extent of aggregation. Even dilute suspensions of blood corpuscles (in physiological sodium chloride solution) agglutinate well, and a subsequent dilution does not destroy the existing agglutination. The reaction is very pronounced in the cold or at room temperature and somewhat weaker at body temperature. An increased electrolyte concentration restrains or inhibits the rouleaux formation while the iso-agglutination is much less suppressed, it may even be promoted (*V. Forssman, Th. Wadstein and G. Fischer, 1930 (119)*).

Those agglutination processes which appear in the cold are called cold-agglutinations. Among these, we must first of all mention the physiological auto-agglutination without haemolysis (*P. Levine, 1928 (251), K. Kettel, 1930 (224), P. Steffan, 1932 (393)*).

In the cold, agglutinin is adsorbed by the erythrocytes and is split off again during a slight increase in temperature. Agglutinin affects not only the individual's own blood corpuscles but also those of other individuals. The most favourable temperature range for auto-agglutination is between  $0^{\circ}$  and  $5^{\circ}\text{C}$ . An increase of the so-called thermo-amplitude, i. e. of the temperature range in which agglutination may occur, is found to take place in a number of morbid states. (For further literature, cf. *P. Levine, 1928 (251)*).

Auto-agglutination as well as iso-agglutination resist moderate dilution with physiological sodium chloride solution. A strict distinction of the cold-agglutinins as auto- or iso-antibodies is not feasible since, as already mentioned in the discussion of auto-agglutination, cold-agglutinins are known which also affect the blood corpuscles of other individuals (cf. the special serological literature).

Furthermore, *Thomsen-Friedenreich's* phenomenon has to be mentioned (*O. Thomsen, 1926 (410) and 1929 (412), V. Frieden-*

*reich*, 1927 (135), *P. Steffan*, 1932 (393), and *E. Witebsky*, 1932 (452) ), *viz.* the unspecific agglutination of stored blood corpuscle suspensions caused by agglutinin which has been produced by the enzymatic effect of certain bacteria.

A number of authors denoted the aggregation of serum-free suspensions of blood corpuscles in isotonic cane sugar-, mannite- or similar solutions as spontaneous agglutination, presumably being the effect of decreased electrolyte concentration, but scarcely a true agglutination (*cf.* § 10 "The effect of the electrolyte content on aggregation", p. 22).

Pseudo-agglutination in a wider sense comprehends all types of agglutinations which might be mistaken for true agglutinations (iso-agglutinations), most frequently, however, the rouleaux formation.

Pseudo-agglutination in a narrower sense includes the disturbed rouleaux formation with irregular, non-rouleaux shaped conglomerates, as found in very marked rouleaux formations as a consequence, for instance, of a high concentration of blood corpuscles, or in a slight dilution of plasma with sodium chloride solution (*cf.* *E. Ponder's* interpretation discussed on p. 41).

The rouleaux formation is quite different from iso-agglutination, primarily because of the lack of absorbable agglutinin. The use of the word agglutination synonymous with rouleaux formation — as done by *Höber's* school — is therefore inadequate.

In a morphological respect, the regular rouleaux formation may be distinguished clearly from the irregular aggregations of the true agglutinations. A slight dilution with physiological sodium chloride solution already diminishes or inhibits rouleaux formation, thus making it clearly distinguishable from iso-agglutination (*S. Hesser*, 1924 (195) ). Even somewhat violent shaking inhibits rouleaux formation. According to most investigators, an increase in temperature accelerates the rouleaux formation (*cf.* the author's divergent meaning, p. 166); cooling down does not counteract the rouleaux formation.

In order to distinguish pseudo-agglutination from true agglutination, *L. Lattes*, 1925 (244), applied suspensions of blood corpuscles in lecithin sol where the corpuscles become spherical and do not form rouleaux. In investigations of rouleaux formation at lower temperature, the cold-agglutination must

certainly be kept in mind, since these processes affect one another in spite of being quite different. According to *O. Thomsen*, 1928 (411), a pronounced rouleaux formation favours the cold-agglutination at room temperature. A given serum showing marked agglutination at room temperature with the blood corpuscles of one individual often exhibits a transition from agglutination to rouleaux formation with the blood of other persons. Heating of the preparation to 35°C (the slide being held over a microburner) causes an immediate cessation of the agglutination which reappears almost completely after cooling down. If this procedure is repeated three or four times, the picture corresponds more and more to a regular rouleaux formation. In certain cases, cold-agglutination fails to appear when the blood corpuscles are kept in lecithin sol inhibiting rouleaux formation which, therefore, must be considered a promoting factor. Some observations similar to *Thomsen's* were made — though not constantly — by *K. Kettel*, 1930 (224). A suspension of erythrocytes in a 3 per cent gelatin salt solution revealed beautiful rouleaux formations; it was not possible, however, to obtain agglutination in this medium and, consequently, these experiments were not suited to support *Thomsen's* assumption.

A detailed review of the literature on the definition of rouleaux formation including especially the older works from this field may be found in *G. Walther's* excellent survey, 1929 (430).

### § 3. WHAT ARE THE FACTORS DETERMINING BLOOD SEDIMENTATION?

#### *Stokes' formula.*

The rate of fall of a small sphere in a viscous fluid can be calculated by means of *Stokes' formula* (cf. § 20 "Colloidal stability etc.", p. 50):

$$v = \frac{2}{9} \frac{(D - d) g}{\eta} r^2 = C r^2, \quad (1)^*$$

where  $v$  is the rate of fall of the sphere,  $D$  and  $d$  are the specific

---

\*) In the following two sections, the mathematical formulas are marked with successive numbers. For the sake of clearness, however, the enumeration of the formulas of section III begins with No. 1. The same applies for section IV.



gravity of the sphere and the medium, respectively,  $g$  is the gravitation constant,  $\eta$  the internal friction of the fluid,  $r$  the radius of the sphere, and  $C$  a constant.

As a simplification, the individual erythrocytes and their aggregates may be considered spherical and, thus, the above mentioned expression is a suitable basis for the discussion of the influence of various physical magnitudes on the sinking reaction (*cf.* the following paragraphs). *Stoke's* modified formula has often been applied to this purpose, first by *R. Fåhræus*, 1921 (109), later by *W. M. Bendien*, *J. Neuberg* and *I. Snapper* 1932 (21), and others, but, as a matter of fact, a quantitative calculation of the blood sinking on the basis of this formula is hardly possible.

#### § 4. THE INFLUENCE OF AGGREGATION (ROULEAUX FORMATION) ON BLOOD SEDIMENTATION.

Table 1 shows clearly that aggregation has by far the greatest influence, since the sedimentation velocity of the conglomerates increases with the square of the radius.

Table 1.

The influence of the aggregation on blood sinking.  
(According to *R. Fåhræus*, 1921 (109)).

Aggregation	Average number of corpuscles per aggregate	<i>S. Odén's</i> equivalent radius*)	Sinking reaction in mm/1 hour
None	1	2,6 $\mu$	0,2
Some	11	5,8 $\mu$	1
Very intense	58000	100 $\mu$	75

\*) See p. 51.

A greater tendency to rouleaux formation produces a more rapid sedimentation (*F. Henle*, 1841 (187) ); the extent of rouleaux formation is proportional to the blood sinking (*R. Fåhræus*, 1921 (109), *V. Siracusa*, 1924 (379), and many others). On the basis of this fact, some investigators (*E. Sahlgren*, 1931 (364), *N. Eklund*, 1931 (101), *P. von der Frappen*, 1938 (122) ) tried to replace the sedimentation reaction by a quicker "agglutination test".

The aggregation is affected partly by the properties of the blood corpuscles and partly by the properties of the plasma. This may be proved by exchange experiments where the blood corpuscles (constant volume concentration) of one individual form a sediment in the plasma of other individuals belonging to the same or to different species, and *vice versa*. (G. Linzenmeyer, 1921 (260), R. Fåhræus, 1921 (109, p. 114), E. Abderhalden, 1922 (1), J. de Corral and I. Villalonga, 1932 (68), J. Zozaya, 1937 (458), R. Bogaert, 1937 (39), E. Gripwall, 1938 (162), G. Trönnberg, 1939 (419), and many others).

The varying sinking velocity of blood of different species is due mainly to a greater or smaller aggregation tendency of the respective erythrocytes (H. Nasse, 1836 (293), V. Siracusa, 1924 (379), Zott, 1930 (459)).

Corral and Villalonga (*loc. cit.*) succeeded in proving the influence of the aggregation tendency by means of exchange experiments with plasma and blood corpuscles of different species. On the basis of their results, these authors differentiated between rapidly or slowly sedimenting blood corpuscles (for instance, horse- and sheep blood corpuscles, respectively).

Independent of the disturbing influence of agglutinins and lysins (*cf.* later), H. L. White and B. Monaghan, 1936 (443), demonstrated this fact producing a sedimentation in an artificial plasma (1 per cent gelatin dissolved in a 0.9 per cent sodium chloride solution which was brought to  $p_H$  7.4 by adding a N/50 phosphate buffer).

Within the same species, the aggregation tendency is almost exclusively determined by the properties of the plasma.

R. Fåhræus, 1921 (109, p. 114), found that blood corpuscles from blood with different sedimentation velocity transferred to the same plasma show the same sinking velocity.

R. Bogaert, 1937 (39), confirmed Fåhræus' results in exchange experiments with blood corpuscles from the stable umbilical vein blood of the foetus and blood corpuscles from the instable blood of the mother.

In rare cases only, the changes of the sedimentation reaction are caused by changes of the surface properties of the erythrocytes (J. G. Stephens, 1938 (394), G. Trönnberg, 1939 (419), and furthermore E. Gripwall, mentioned p. 13).

All factors promoting aggregation increase the sinking velocity\*). Through exchange experiments with plasma and erythrocytes from different anaemia patients *etc.* it is clear that blood of the same blood groups must be employed, since the specific haemagglutination also increases the sinking velocity. (*I. Freuchen*, 1926 (124), *F. Sander* and *M. Sander*, 1939 (365)).

According to *H. Reichel*, 1936 (351), the different sizes of the erythrocyte aggregates must be considered the cause of the diffuse interface (*cf.* p. 40) found at relatively high sinking velocities. (For further literature, *cf.* *E. Gripwall*, 1938 (162)).

## § 5. THE INFLUENCE OF SHAPE, SIZE, AND SPECIFIC GRAVITY OF THE BLOOD CORPUSCLES.

Changes in shape, size, and specific gravity of the erythrocytes are only of negligible importance compared with rouleaux formation.

From ancient times (*J. Lister*, 1858 (263), *M. Heidenhain*, 1904 (184)), the disc form of the erythrocytes was considered the main condition for rouleaux formation. *L. Lattes*, 1925 (244), emphasized that an alteration of the shape in the direction of spherocytosis, where the contact surfaces are reduced, inhibits rouleaux formation.

Neither the slightly biconvex, nucleated blood corpuscles of the frog (*Lister*, *Ranvier*) nor the young erythrocytes (normoblasts) form rouleaux (*R. Beneke*, 1913 (23), *J. G. Stephens*, 1938 (394), *E. Gripwall*, 1938 (162)). Spherical erythrocytes in hypotonic salt solutions (*Robin*, 1858 (355)) or in blood which had been stored for some time (*Lattes*) do not aggregate. Thorn-apple shaped erythrocytes (*i. e.* because of the hypertonia of the suspension fluid) lose their aggregation ability (*L. Lattes*, 1925 (244), *Willshire*, 1912/13 (451)).

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\*) *Addendum*: In rare cases, a vastly increased sedimentation rate may be caused by pathological cold-agglutination. This may be proved by direct microscopy of the blood and by a comparison of the sedimentation tests at room temperature and at 37° C. If the increased sedimentation rate is due to cold-agglutination, the rate of sinking will decrease instead of increase with increasing temperature (*cf.* *C. U. Jessen* and *J. Bing*, *Acta med. scand.* 105, 279, 1940).

*Vanlair* and *Masius*, 1871 (427), observed a lack of rouleaux formation in a case of icterus haemolyticus with spherocytosis. However, the aggregation of the spherocytes which characterize the hereditary haemolytic icterus has been observed by *E. Gripwall* (162) who was especially interested in this phenomenon. In the case of haemolytic jaundice, a varying tendency to rouleaux formation was found, but the more pronounced the spherocytosis, the more atypical is the microscopic picture. Because of the altered shape of the cells, the erythrocytes cannot form piles of coins, but cluster together to greater or smaller coarse conglomerates containing corpuscles of varying shapes, *viz.* bell-shaped and pear-shaped corpuscles. The increased sinking reaction present in numerous cases of haemolytic icterus must be caused by an increased aggregation tendency; during the haemolytic crisis, the sinking velocity is increased. By means of exchange experiments, *Gripwall* succeeded in proving that the increased aggregation tendency originated from changes of the surface properties of the erythrocytes.

During aniso- and poikilocytosis, the rouleaux formation becomes irregular but is not completely inhibited (*Wiltshire*, 1912/13 (451)).

In agreement with *Stokes'* modified formula, greater erythrocytes sediment more rapidly than smaller ones (*K. Bürker*, 1922 (61), and others).

With increasing content of carbon dioxide in the blood, the erythrocytes increase in size and they approximate the spherical shape; in spite of this fact, the sinking is reduced. The influence of the shape on the aggregation has already been described, the effect of the carbon dioxide content on the blood viscosity will be discussed later (p. 27).

According to *Stokes'* formula, the sedimentation velocity of blood corpuscles and their aggregates is proportional to the difference in specific gravity relative to that of the plasma. If the sedimentation is accelerated by centrifuging, the difference in specific gravity is more obvious. Taking the same erythrocyte volumina from different heights of a centrifuged blood sample and suspending them in plasma, *E. Abderhalden*, 1922 (1), found an increased sinking velocity of the erythrocytes from the bottom of the centrifuge tube.

*M. Bönninger* and *W. Herrmann*, 1924 (45), investigated pernicious anaemia blood and found the greatest cells and those rich in haemoglobin at the point of the centrifuge tube. The experiments of these authors led to the same results as *Abderhalden's*. In pernicious anaemia, the specific gravity of the blood corpuscles is always increased while it is often decreased in the case of simple, secondary anaemia. (*C. Oestreich*, 1931 (306), and *G. A. Lindeboom*, 1934 (256) ).

In a suspension of red blood corpuscles in *Hayem's* solution, where the aggregation is annulled, the sinking speed at a constant cell volume was proportional to the index colorimetricus (*M. Ohno*, 1926 (308), *W. Bendien*, *J. Neuberg* and *I. Snapper*, 1932 (21) ); the empirical formula for the rate of sedimentation includes the colour index as a constant.

The specific gravity of normal erythrocytes varies between 1.085 and 1.094 at 18°C. (The figures are taken from *Bendien*, *Neuberg* and *Snapper* (21) who also discussed the blood sinking on the basis of *Stokes' formula*). The specific gravity of the plasma varies between 1.025 and 1.026. The difference of the specific gravities, *D-d* of *Stokes' formula*, is thus 0.065. In cases of severe pernicious anaemia, the specific gravity of the plasma may decrease to 1.022 and that of the erythrocytes may occasionally increase to 1.100, *D-d* = 0.088. In a secondary anaemia with the plasma specific gravity 1.022 and the erythrocyte specific gravity 1.068, *D d* becomes 0.046. The variations of the factor *D-d* are thus not quite unessential.

## § 6. THE INFLUENCE OF THE ERYTHROCYTE CONCENTRATION (WITH A POSSIBLE CORRECTION).

The concentration of the blood corpuscles essentially determining the viscosity of the whole blood is of great influence on the sedimentation test.

Already *R. Fåhræus* (109) emphasized that the sinking reaction decreases or increases with increasing or decreasing amounts of blood corpuscles; numerous authors, among whom *M. Bönninger* and *W. Herrmann*, 1923 (44), *A. Westergren*, 1924 (436, p. 628), *H. C. Gram*, 1928 (159), *M. D. Rourke* and *A. C. Wetene*, 1930 (360), and *A. C. R. Walton*, 1933 (431) being

the most important names, attempted to correct the sinking reaction for the variation in the erythrocyte concentration.

While many authors thus realized the influence of the number of erythrocytes on the sinking reaction because of changes in viscosity of the whole blood, only a few (*A. Sellards*, 1908 (376), *E. Ponder*, 1926 (333)) understood that also the rouleaux formation is affected by changes of the erythrocyte concentration. In other words, an alteration of the blood corpuscle concentration changes both the extent of aggregation of the erythrocytes and the viscosity of the whole blood. Finally, it is clear that the extent of aggregation in various plasmas — due to the different aggregation capacity — varies with the erythrocyte volume.

The principle of *H. C. Gram's* method of correction (159) is so fine that it seems worth while discussing it in detail.

*H. C. Gram* plotted a series of empirical curves by determining the 1 hour sinking of blood samples with different sedimentation velocities at different volume concentrations of the erythrocytes, the latter being produced by diluting the blood with its own plasma. The results were plotted in a coordinate system with the sinking velocity in mm. as axis of ordinates and the cell volume per cent — expressed by per cent of haemoglobin — as axis of abscissae.

At a given volume per cent (or per cent haemoglobin, respectively) a given extent of erythrocyte aggregation corresponds to a well-defined sinking. The empirical curve through the point corresponding to this sinking and volume per cent corresponds to a given aggregation capacity of the plasma.

The performance of the correction: The 1 hour sinking of the blood sample and the volume per cent of the cells is determined (the latter by means of the haemoglobin per cent). The empirical curve through the point corresponding to the measured sinking and volume per cent is found, and this curve is followed to the point of intersection with the correction line which corresponds to 43 volume per cent. There, the corrected sinking is read directly.

Thus, *Gram's* results are valid in the case of blood samples showing the same sinking velocity at the same haemoglobin per cent (volume per cent). A comparison of the corrected sinking velocity of different blood samples and their true sinking at 43 volume per cent showed good agreement of the results.

In a later paper from 1929 (160), *Gram* attempted to employ the correction method on a greater clinical material. According to the early observations by *F. Bennighof*, 1921 (24), and the recent investigations by *A. Westergren*, *H. Theorell* and *G. Widström*, 1931 (437), *H. Lebel* and *M. C. Lottrup*, 1933 (246, 247), *H. Reichel* and *van de Stadl* (352), the non-corrected sinking represents more satisfactorily the clinical state of the patients than the corrected sedimentation value.

In spite of the fact that the correction method seems to be less applicable to clinical work, its scientific value is indisputable, since the method in a simple way takes into account both principal factors of the sinking reaction: the erythrocyte aggregation and the internal friction of the total suspension.

In the technique usually applied to blood letting, where a certain amount of citrate or oxalate solution is added to a given volume of blood in order to prevent coagulation, the electrolyte content of the plasma and its dilution with respect to the protein content is changed due to the different cell volume. However, these circumstances will be of great importance, since the aggregation is markedly sensitive to electrolytes (*cf.* p. 22).

In order to improve *H. C. Gram's* correction method, *M. Jersild*, 1934 (213), has developed a new method with special regard to the electrolyte content, where the sinking velocity is measured directly at 43 volume per cent of erythrocytes.

## § 7. THE VISCOSITY OF THE WHOLE BLOOD.

Since the whole blood forms the medium in which the aggregates sediment, the viscosity of the whole blood and not that of the plasma must be introduced into the formula of the sedimentation velocity; nevertheless, the formula remains valid, as stated by *E. Cunningham*, 1910 (72). (*cf.* the detailed discussion of *Stokes' formula*, p. 52).

While the viscosity of normal blood is about 4.5, the viscosity during anaemia can decrease to 2.0 and during polycythemia it can increase to 6.0. The relative viscosity of the plasma amounts to 1.7—2.0, the absolute viscosity of water, which forms the unit of the relative measure, being 0.0106 Poise at 18°C.

The viscosity of the blood is primarily determined by the

volume concentration of the erythrocytes and by the viscosity of the plasma; furthermore, it depends upon the gas content of the blood and on the special properties of the red cells.

Within a wide range, *J. W. Trevan*, 1918 (418), found proportionality between the viscosity of the blood and the plasma as long as the volume concentration of the erythrocytes was kept constant.

The immense significance of the number of blood corpuscles for the viscosity of the whole blood has been understood by numerous investigators. With increasing number of erythrocytes the viscosity increases rapidly.

In agreement with *A. Einstein's* mathematico-physical viscosity formula for suspensions, (1906 (96) and 1911 (98)),

$$\frac{k^*}{k} = 1 + 2.5 \phi, \quad (2a)$$

where  $k^*$  and  $k$  are the friction coefficients of the suspension and the fluid, respectively, and  $\phi$  is the volume per cent of the suspended material, the viscosity is not only a function of the number of particles but dependent on the volume concentration.

In the case of concentrated emulsions, *E. Hatschek*, 1920 (181), obtained the following equation:

$$k^* = k \frac{1}{1 - \frac{2}{3}\phi} \quad (2b)$$

taking into account the deformation of the drops in the disperse phase and the displacement of the liquid in the thin layers between the drops. *J. W. Trevan*, 1918 (418), and later *E. Hatschek*, 1920 (181), found this formula to fit rather well the properties of suspensions of blood corpuscles.

The viscosity of the disperse phase does not enter *Hatschek's* formula (*in casu* blood corpuscles) which, however, involves the condition that the particles are readily deformable.

*L. Berczeller* and *H. Wastl*, 1924 (29), found a suspension of yeast cells in serum to have a much greater viscosity than blood corpuscle suspensions in the same serum and at the same volume concentration. This result indicates that elasticity and deformability of the particles play an enormous part in the viscosity of suspensions.



R. W. Hess, 1910 (192) and 1912 (193), was the first to prove the varying resistance of flow at low pressure, or rather at a lower flowing velocity; at high pressure, i. e. rapid flow, he found *Poiseuille's* law to be valid in the case of blood.

Considering the properties of colloidal solutions, W. Ostwald, 1924 (320), differentiated between a pressure-independent, normal viscosity and a pressure-dependent "structural-viscosity".

The viscosity of the blood decreases gradually from 15 °C to 37 °C. E. Rothlin's detailed investigations, 1920 (359), revealed that the effect of temperature fluctuations was most marked at a low pressure of flow since structural viscosity — more than normal viscosity — depends upon temperature.

The elastic deformation of the blood corpuscles during rapid flow found by F. Frimberger, 1938 (137), in his experiments on the fixation of flowing blood and interpreted by him as the cause of the structural viscosity is of no interest for the viscosity phenomenon in blood sinking.

At the very slow flowing which is of importance to blood sedimentation we can scarcely set aside the fact that the disaggregation of the erythrocyte conglomerates and the following orientation of freely dispersed red cells caused by the movement of the fluid must appear as energy consuming processes and consequently must participate in the structural viscosity.

The possible significance of different degrees of aggregation for the viscosity of the whole blood is not yet quite clear. One might assume that the viscosity of the suspension increases with increasing aggregation because the conglomerates occlude plasma. L. Berczeller and H. Wasil, 1924 (29), made the most important observation that blood flows much quicker after repeatedly having passed a viscosimeter; analogous observations were made on different colloids. Especially the result of the first measurement deviated markedly from the later values which showed a slight decrease in the measured times of passage from experiment to experiment, presumably due to a change of the size of the erythrocyte aggregations.

Measurements of the viscosity of the blood under the same conditions as present in the sedimentation of blood corpuscle aggregations in the sinking reaction are difficult or almost impossible

to perform, since a change of the circumstances is inevitable during the attempt to measure viscosity.

Finally, the well-known phenomenon of increased viscosity as a consequence of an increased carbon dioxide content of the blood should be mentioned. Increased carbon dioxide content enlarges the volume of the erythrocytes; increasing saturation with oxygen causes a decrease in the viscosity of the blood.

## § 8. THE INFLUENCE OF VISCOUS SUBSTANCES ON BLOOD SEDIMENTATION.

### *Plasma viscosity.*

Besides the plasma proteins fibrinogen and globulin, a number of other viscous substances cause erythrocyte aggregation which may be observed either when red blood corpuscles are suspended in isotonic salt solution and varying amounts of the viscous material are added ("artificial plasma"), or when this substance is added to the blood. Some of these colloids are gelatin (*Weidenreich*, 1905 (434), *R. Fåhræus*, 1921 (109), *F. von Krüger*, 1923 (235)), gum arabic (*H. Nasse*, 1836 (293), *F. Frimberger*, 1938 (138)), casein (*R. Fåhræus*, 1921 (109)) tragacanth (*Wiltshire*, 1912/13 (451), *B. Swedin*, 1936 (407)), salep, thymonucleic acid (*B. Swedin*, 1936 (407)), and many others. An increase in the plasma viscosity by addition of one of the mentioned substances produces a paradoxical increase in the sinking reaction, since the retarding influence of the plasma viscosity (viscosity of the whole blood) is surpassed by the effect of the highly increased aggregation tendency.

*H. Nasse*, 1836 (293), already familiar with the favourable effect of gum arabic on the sinking velocity, stated "Gummi ersetzt also die Stelle des klebrigen Faserstoffs".

*D. von Klobusitzky*, 1925 (227) and 1929 (228), who investigated the influence of electrolytes on the sinking reaction, arrived at the result that the anions of *Hofmeister's* salts affect the plasma viscosity to the same extent as the blood sinking.

*F. von Krüger*, 1923 (235), studying the sinking at different gelatin concentrations, emphasized that the maximum of the

sinking velocity depends not so much on a certain gelatin concentration as on the degree of viscosity.

*F. Frimberger*, 1938 (138), proved that the sinking is proportional to the viscosity of the suspension fluid so that the chemical nature of substances as gelatin, gum arabic, and vinarol\*) cannot be the essential point in their promoting effect on aggregation. A given colloid concentration does not always produce the same degree of aggregation. After long-lasting boiling of the gelatin solution (without changing the concentration) and after ultra-violet irradiation of gum arabic solutions, the viscosity and the sinking promoting effect were reduced. Ageing plasma decreases its viscosity and its ability to produce agglutination.

*R. Ley*, 1922 (254), observed, the more rapid a sinking, the more viscous the plasma.

*R. Fåhræus* (109) found fibrinogen which markedly promotes aggregation to be more viscous than albumin. Furthermore, he pointed out that the viscosity of the serum and its aggregation capacity are increased by a thermal treatment at higher temperature. Heating serum to 56—60 °C, *L. Moll*, 1904 (278) and 1905 (279), noticed an increase in the globulin fraction at the cost of the albumin fraction. Similar changes of the properties of the serum proteins (salting-out conditions) were found by *A. Fischer*, 1932 (118), *A. Schmitz* and *A. Fischer*, 1933 (371), after addition of heparin, and by *M. Chr. Ehrström*, 1939 (94), after addition of the calcium salt of chondroitin sulfuric acid. In agreement with the change of the properties of the serum proteins after addition of heparin, *H. Stortz* and *H. Schlungbaum*, 1933 (403), and *K. W. von Kaulla*, 1939 (223), proved an increased sinking reaction (the opposite result was found by *K. Zirm* and *G. Scherk*, 1933 (457)).

*M. Chr. Ehrström* (94) found an increase in the serum viscosity and the sedimentation reaction of the blood after addition of heparin or the calcium salt of chondroitin sulfuric acid.

In connection with the changed salting-out conditions of the proteins after the above described interferences, it seems opportune to mention the frequently discussed parallelism between sinking reaction and different "lability reactions" (*Takata-Ara*, *Matéfy* and others) of the serum proteins (*W. Bendien*, *J. Neuberg* and

\*) A preparation from *I. G. Farben* of a constitution unknown to the author.

*I. Snapper* (21) ). However, the phenomena are not at all simple; with regard to the *Takata-Ara* reaction, *cf.* *A. van Meeteren*, 1937 (275), and *A. de Vries*, 1938 (428).

The cause of the ability of emulsoids to produce erythrocyte aggregations is in fact quite unknown (*cf.* below, p. 43).

Not all viscous substances produce erythrocyte aggregation as observed primarily on albumin (*R. Fåhræus* (109) ) and, furthermore, on the sodium salt of yeast nucleic acid (*G. Linzenmeyer*, 1921 (260), *B. Swedin*, 1936 (407) ).

In isotonic salt solutions of viscous substances such as gelatin (*R. Fåhræus* (109) ) the erythrocytes maintain their disc shape (*cf.* § 17 "Factors determining the shape of the erythrocytes", p. 33).

The relative viscosity of the plasma depends upon the protein fractions and varies between 1.5 and 2.5, the influence of the plasma viscosity on the viscosity of the whole blood being less pronounced than that of the erythrocyte concentration.

## § 9. PLASMA CONSTITUTION. PROTEINS.

It has already been mentioned (p. 11) that the properties of the plasma primarily determine the degree of aggregation at a given erythrocyte concentration.

With respect to the influence on the blood sedimentation of the single constituents of the plasma (§§ 8—12) a comprehensive literature exists, and the author may therefore confine himself to refer to the reviews mentioned on p. 6.

Fibrinogen and globulin promote the blood sedimentation while albumin acts as a suppresser. *A. Westergren*, *H. Theorell* and *G. Widström*, 1931 (437), and furthermore *W. Bendien*, *J. Neuberg* and *I. Snapper*, 1932 (21), gave a formula suited for an approximate calculation of the sedimentation reaction if the protein fractions are known. *W. Bendien* and *I. Snapper*, 1931 (22), disputed the influence of the albumin fraction upon the sinking, while *I. v. Zarday* and *G. Farkas*, 1931 (456), found the sinking to be inversely proportional to the amount of albumin (and proportional to the fibrinogen- and globulin content). A survey of the protein spectrum at various diseases may be found in the

papers by *W. Starlinger* and *E. Winands*, 1928 (389, 390, 391, 392).

In most cases of increased sinking speed, the amount of fibrinogen is increased more than the amount of globulin. Sometimes (for instance in the case of liver cirrhosis), the sinking is vastly increased, in spite of the fibrinogen content being normal or even decreased. However, in this case the amount of globulin is increased. A high sedimentation reaction in defibrinated blood is almost constantly associated with a great increase in the globulin content.\*) Since, however, the sinking velocity depends on both the amount of fibrinogen and of globulin, the ratio albumin:globulin is without any significance for the sinking reaction (*M. Leffkowitz*, 1932 (249, p. 176) ).

## § 10. THE EFFECT OF THE ELECTROLYTE CONTENT ON AGGREGATION.

*H. Nasse's* knowledge of the suppressing effect of salts on the aggregation (1836 (293) ) has already been discussed on p. 4.

*Gürber*, 1904 (165), was presumably the first to discover that ox corpuscles are able to aggregate even after the serum has been washed off with an isotonic saccharose solution. After storing in the cold for 10 hours, a disaggregation occurred. According to *Gürber's* investigations, the aggregation is closely connected with the salt concentration in the suspension fluid. Minute amounts of salt (0.5 per mille NaCl or 0.01 per mille  $\text{Na}_2\text{CO}_3$ ) already inhibit the appearance of aggregations or destroy existing aggregations.

*W. Radsma*, 1918 (344), was aware of the fact that the blood corpuscles can be brought to cluster if a relatively great amount of isotonic glucose solution is added to the blood. This aggregation could be annulled by addition of small amounts of salt. Arranging the salts according to their effectiveness, the anions showed the same sequence as in *Hofmeister's* ionic series.

By means of electro-dialysis, *B. Swedin*, 1936 (407), succeeded in producing aggregation of ox corpuscles in a saccharose solution.

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\*) *Addendum*: By means of the formol-gel-reaction, we may estimate whether the plasma proteins or other factors cause the increased sedimentation (*J. Bing* and *C. U. Jessen*, *Acta med. scand.* 105, 273, 1940).

The degree of aggregation increased with decreasing amount of electrolyte measured by its electric conducting property. The microscopical investigation revealed completely irregular aggregates and the absence of rouleaux formations, presumably because of a changed erythrocyte form. (About this latter point, however, no details are given in the cited paper). After addition of sufficient amounts of electrolyte, a momentary dispersion appeared in the flocculous suspension.

Blood corpuscle suspensions in a saccharose solution containing some  $\text{CaCl}_2$  showed a remarkable stability to electro-dialysis.

30 times the quantity of electrolyte sufficient for the disaggregation of electro-dialyzed pure blood corpuscle-saccharose suspensions was necessary for the disaggregation of conglomerates in saccharose solutions containing a viscous substance as, for example, gum arabic, tragacanth, thymonucleic acid, and others.

It was not feasible in a quantitative analysis to discover any adsorption of electrolytes or viscous substances to the blood corpuscles.

When calculating the electrolyte surface in an electro-dialyzed suspension, *Swedin* showed that the amount of Na- or K-ions in a hydrated state necessary to produce disaggregation was just sufficient to cover the blood corpuscles with a monomolecular layer.

*J. de Haan*, 1918 (169), corroborated the well-known view that the rapid sedimentation of horse blood is caused by an intense rouleaux formation and he found that diluting the blood with physiological NaCl-solution resolved the rouleaux into single blood corpuscles.

The effect of various electrolytes on diluted blood corpuscle suspensions has been investigated among others by *L. Berczeller* and *E. Stanker*, 1917 (25), *P. György*, 1921 (168), *J. Runnström*, 1921 (362), *F. Raue*, 1922 (350), *G. Ehrismann*, 1923 (93), and *D. von Klobusitzky*, 1925 (227) and 1929 (228). The sinking velocity decreased with increasing electrolyte concentration in such a way that the effect of the anions followed their position in *Hofmeister's* ionic series, while that of the cations was irregular and varied with the experimental conditions.

In concentrated suspensions, *B. Enockson*, 1931 (106), observed an improved stability after addition of NaCl. Glucose and NaCl,

added in suitable amounts, produced a marked reduction of the sinking velocity.

The effect of calcium salts, already mentioned in connection with *Swedin's* electro-dialysis experiments, was studied by *M. P. Demurtas*, 1932 (82), who found in numerous cases an increased sinking after intravenous injection of  $\text{CaCl}_2$ ; sometimes, however, the same author noticed a suppressing effect. Exchange experiments made it evident that an ion displacement in the erythrocytes also affected the sinking reaction. On account of the complicated equilibrium states of the salts, a change in the concentration of the salts may increase as well as decrease the sinking.

After intravenous injection of calcium chloride into animal organisms, *M. Georgopoulos*, 1926 (149), observed an increased blood sinking. In most cases investigated, *F. Bachman* and *K. Bahn*, 1924 (19), proved a reduced sinking and a simultaneous reduction of the viscosity and of the protein content together with an increased calcium level. *J. Runnström*, 1921 (362), noticed a greater stability after addition of calcium and barium salts than after addition of sodium and potassium salts. According to *Uehara*, 1929 (424), an increased calcium level is generally accompanied by a slower sinking, in analogy to intravenous injections of calcium chloride or addition of the same salt *in vitro*.

## § 11. THE INFLUENCE OF LIPOIDS ON BLOOD SINKING.

The effect of plasma lipoids upon blood sedimentation is disputed but evident.

By adding cholesterin and lecithin suspensions to the blood *in vitro*, *H. Kürten*, 1920 (237), proved the antagonistic effect of these substances upon the blood sinking. The microscopic investigation of cholesterin blood revealed a pronounced rouleaux formation, while the thorn apple shaped corpuscles of the lecithin blood were spread over the whole field of vision.

*H. Theorell*, 1930 (409), studied thoroughly the properties of plasma lipoids and, furthermore, *H. Magistris*, 1931 (269), cited a number of older, not very elucidative papers from this field.

The method of preparing cholesterol- and lecithin suspensions seems to be the salient point of the whole problem.

*Theorell* was able to show that the total cholesterol and phosphatide content of the plasma is without any influence on the sedimentation reaction; the ether extractable cholesterol, however, had a vastly suppressing effect. The same author discussed the significance of a lipid linkage to the proteins.

In contradistinction to *Theorell*, *B. Ohlson* and *O. Rundquist*, 1932 (307), reported that an extraction of the plasma lipoids without noticeable change of the proteins does not cause any alteration of the sinking reaction. However, the method of extraction applied — precipitation with alcohol in the cold followed by a treatment with ether in a Soxhlet apparatus — seems to be a somewhat violent treatment of the sensitive proteins.

*B. Swedin*, 1933 (406), investigated the sinking reaction, the protein fractions of the plasma, and the amount of easily extractable cholesterol on different animals. It could be proved that horse- and ox blood, showing greatly different sinking velocities (high and low, respectively), have similar plasma protein fractions, while the amount of extractable cholesterol is considerably smaller in horse plasma than in ox plasma. As regards the relation between the cholesterol content of the erythrocytes and their isoelectric point, their cataphoretic velocity (at the  $p_H$  of the blood), and their ability to aggregate, *cf.* the present paper, p. 44.

A corroboration of *H. Kürten's* result, 1920 (237), was given by *J. Zozaya*, 1937 (458), who found that the addition of lecithin (as a suspension) markedly suppresses the blood sedimentation, while cholesterol acts slightly promoting. The microscopic investigation revealed, in the first case, dispersion and change of the shape of the erythrocytes (to the spherical shape), in the second case, increase in rouleaux formations (*cf.*, furthermore, *R. Hirohata* and *H. Shimokawa*, 1935 (200), measurements of the sinking speed and cataphoresis, mentioned on p. 41 of the present paper).

While the rouleaux formation is annulled by addition of lecithin, the iso-agglutination remains unaffected (*cf.* p. 8. About the antagonism between cholesterol and lecithin, *cf.* p. 34).



In connection with *B. Bergenhem* and *R. Fåhræus*' interesting discovery of a lecithinase present in the blood, 1936 (31), (*cf. B. Bergenhem*, 1938 (30)), and transferring lecithin into lysolecithin which has a markedly stabilizing effect on the blood, we may expect that a further investigation of the influence of the lipoids on the blood sinking will reveal elucidative results.

## § 12. THE INFLUENCE OF THE GAS CONTENT OF THE BLOOD ON THE SEDIMENTATION TEST.

Most investigators agree that the different content of oxygen and carbon dioxide in arterial and venous blood is not of decisive influence upon the sinking reaction (*G. Leendertz*, 1921 (248), *A. Westergren*, 1924 (436), *M. Georgopoulos*, 1926 (149), *H. Reichel*, 1936 (351), and the authors of numerous micro-methods).

*F. Kok*, 1923 (229), found generally a higher sinking reaction in arterial than in venous blood, while *W. Hess*, 1921 (194), obtained this result only exceptionally.

According to *A. Westergren* (*loc. cit.*), a short stasis (1—2 min.) before bleeding does not cause any change of the sinking reaction.

In experiments *in vitro*, *G. Leendertz* (248), *L. Berczeller* and *H. Wastl*, 1923 (26), *W. Ito*, 1924/25 (210), and others found that an increase in the  $\text{CO}_2$ -content causes a delay in the sinking velocity, while an  $\text{O}_2$ -increase accelerates the sinking speed. During experiments *in vitro*, the influence of variations in the gas concentration on the sedimentation reaction is considerably greater than the physiological variations (*Leendertz, loc. cit.*); the reduced sinking due to increasing  $\text{CO}_2$ -content can be compensated by a supply of oxygen ( $p_H$ , *cf. later.*).

*H. Rogel* and *L. Binet*, 1925 (356), using dogs as test animals, found a more rapid sedimentation in arterial than in venous blood. During mechanical asphyxia, the sinking reaction of the arterial blood decreased, while hyperventilation increased the sinking. The variations in the sinking reaction were due to variations in the erythrocyte volume which increases in blood rich in carbon dioxide.

According to *L. Berczeller* and *H. Wastl* (*loc. cit.*), the sinking reaction of oxygen-saturated blood is always higher than the

sinking reaction of venous blood. For scientific investigations, these authors therefore recommend the employment of blood which is saturated with a given gas in order to obtain reproducible conditions.

Apart from a number of changes caused by variations of the electrolyte equilibrium *etc.* (*H. J. Hamburger*, 1902 (173)), the increasing content of carbon dioxide gives rise to an increase in the cell volume and the viscosity of the whole blood. The blood corpuscles become more spherical, presumably in disfavour of the aggregation.

*Odaira*, 1921 (301), pointed out that an increase in the oxygen content produces a decreased blood viscosity, while the erythrocyte volume remains unchanged. The increase in the oxygen concentration causes an increased hydrogen ion concentration of the blood, thus rendering the situation rather complicated.

It is apparent that the aggregation of blood corpuscles is affected by decisive changes in the physico-chemical properties after saturation with oxygen or carbon dioxide. *Berczeller* and *Wastl* supposed that oxygen promotes aggregation. Slow sinking reactions were frequently observed in cases of dyspnoea and cyanosis (*cf.* the reviews p. 6); apart from carbon dioxide augmentation, anoxaemia, increase in erythrocyte volume, and total viscosity of the blood, the composition of the plasma is changed with respect to proteins, salts, and water (hydraemia).

As regards the dependence of the sinking reaction on the blood  $p_H$ , we lack systematic investigations with a uniform and accurate technique. The optimum of the aggregation seems to be in the alkaline  $p_H$  region. *Kylin*, 1938 (238), pointed out that a lowering of  $p_H$  suppresses the sinking. The few investigations of alkali reserve and sinking reaction (*S. Moschini*, 1933, (283)) yet available do not permit any reliable conclusions.

### § 13. THE EFFECT OF SOME OTHER SUBSTANCES ON BLOOD SINKING.

In the present paragraph, the effect of a number of different substances on blood sinking will be discussed; these substances may best be arranged in the following groups:

- I. normal constituents of the blood appearing in abnormal amounts;
- II. abnormal constituents of the blood which (in noticeable amounts) appear only in various pathological states;
- III. foreign substances added to the blood for experimental purposes.

I. Urea. Increased rest nitrogen causes a strong increase in the sinking reaction (*Ch. Achard, A. Codounis and E. Hadji-georges, 1931 (10)*). In the case of uraemia, especially high values of the sinking reaction are observed.

Glucose. The observations on the sinking reaction in cases of diabetes mellitus are rather contradictory; in uncomplicated cases of diabetes, the sinking reaction is said to be normal (for literature, *cf. H. Reichel, 1936 (351)*).

II. Components of the bile. According to *M. E. Alexander, 1924 (15)*, the addition of bile or duodenal juice *in vitro* has a pronounced inhibiting effect on blood sinking. This suppression is caused especially by the salts of the bile acids, while bilirubin is without any influence (*G. Katz and P. Radt, 1927 (222)*). *A. Radosavljević and M. Sekulić, 1932 (343)*, proved a temporary suppression of the sinking after intravenous injection of salts of bile acids and they found most of these salts (about 60 per cent) bound to the erythrocytes.

As regards further literature on the sinking reaction in cases of icterus, *cf. H. Reichel (351)* and *G. Trönnberg, 1939 (419)*. The increased sinking during icterus haemolyticus (*E. Gripwall, 1938 (162)*) has been mentioned on p. 13. In the greater number of cases of icterus, we find a relatively low sinking reaction. *G. Trönnberg's* exchange experiments (419) are in favour of the interpretation that the suppressed sinking in certain types of hepatitis originates from the properties of the plasma. In some cases of icterus, a decreased tendency of the erythrocytes to aggregate was found, apparently in parallelism to *Meulengracht's* icterus index. It is justifiable to interpret the effect of bile acids upon blood corpuscles as a stabilization, however, the observation of cases with high icterus index and without suppression of the sinking are against this interpretation.

III. *W. Bendien, J. Neuberg and I. Snapper (21)* were able to

prove that sodium salicylate reduces the sinking, while sodium benzoate is without any effect.

According to *M. Chr. Ehrström*, 1939 (94), methylene-blue and toluidine-blue inhibit the blood sinking. *A. V. Ferrari*, 1938 (117), found that "electro negative" colloidal dye-stuffs hinder the blood sinking *in vitro* as well as *in vivo*. With regard to the symbatic variation of sinking reaction and cataphoretic velocity (which will be discussed later, *cf.* p. 41), the measurement of the electrokinetic potential would be of greatest importance.

*P. Hinteregger*, 1931 (199), pointed out that the sinking is not affected by haemolytica; in contradistinction to this, *B. Bergenhem*, 1938 (30), emphasized that the erythrocyte ability to aggregate is reduced and, consequently, the blood is stabilized by haemolytica.\*)

*G. Linzenmeyer*, 1920 (258), observed a suppression of the sinking reaction after addition to the blood of amyl and heptyl alcohol, isobutyl urethane and other narcotics.

Finally, a number of colloids and stabilizers have been mentioned earlier.

#### § 14. THE TEMPERATURE EFFECT UPON THE SINKING REACTION.

In the consideration of the influence of temperature on the sedimentation test we must differentiate between

- I. reversible changes due to the temperature at which the blood sinking is determined;
- II. irreversible changes produced by temperature action upon the blood, the so-called thermal stabilization;
- III. under certain circumstances, both I and II must be taken into consideration.

*Ad I.*

As the result of numerous investigations, it must in principle be considered to be proved that cooling down reduces the sinking

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\*) *Addendum*: Also *C. U. Jessen* and *J. Bing*, *Acta med. scand.* 105, 279, 1940, state that saponin annuls rouleaux formation; cold-agglutination, however, is not affected.

while heating promotes the blood sinking. (*R. Fåhræus*, 1921 (109), *R. Ley*, 1922 (254), *J. Josefowicz*, 1922 (216), *A. Westergren*, 1924 (436), *I. Freuchen*, 1925 (123), *M. Georgopoulos*, 1926 (149), *M. B. Gordon* and *D. J. Cohn*, 1928 (153), *R. Rimini*, 1934 (354), and many others). Occasionally, the opposite result was found, especially in pathological blood, as described for example by *K. Löwenberg*, 1924 (265), *K. Stöcklin*, 1926 (404), and *J. M. Henderson*, 1929 (186).\*)

The alteration of the sinking reaction is not constant; *A. Westergren*, 1924 (436), and *M. D. Rourke* and *E. D. Plass*, 1929 (361), showed that higher temperature was of greater promoting effect than lower temperature.

The dependence of the blood sinking on temperature is presumably connected with a change in the plasma viscosity (*E. Ponder*, 1925 (332)). Apart from the change in the plasma viscosity (and the viscosity of the whole blood) which is presumably of the greatest importance, the temperature effect of the erythrocyte aggregation must also be taken into account. If the aggregation increases with increasing temperature — as shown by *Bub*, 1906 (49), and *E. Ponder*, 1926 (333), who found an increased rouleaux formation after slight heating and a rapid rouleaux formation at 37 °C — this phenomenon will favorize the effect of a reduced viscosity.

The influence of temperature on the viscosity of the whole blood has been investigated by *E. Rothlin*, 1920 (359), (*cf.* already p. 18).

When dealing with blood to which viscous, sedimentation-increasing substances were added, *G. Walther*, 1929 (430), observed that the aggregation of blood containing gelatin increased proportionally to the temperature, while solutions containing gum arabic showed the opposite behaviour.

## Ad II.

*R. Fåhræus* (109) observed that disc shaped erythrocytes were changed into spherical types and their tendency to aggregate

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\*) *Addendum*: *C. U. Jessen* and *J. Bing*, *Acta med. scand.* 105, 279, 1940, report one case of hyperautoagglutininæmia (pathological cold-agglutination) in which the sedimentation test was lower at 37° C than at room temperature.

was decreased or inhibited as soon as unstirred blood was heated to 30—42.5 °C. The effect failed to appear when the blood was stirred during heating.

In further investigations, *B. Bergenhem* and *R. Fåhræus*, 1936 (31), and *B. Bergenhem*, 1938 (30), found that the increased stability of the blood (the so-called thermal stabilization) was due to an alteration in the serum produced by an enzymatic process with the serum phosphatides as substrate (these authors give a detailed review of the earlier literature). Under the effect of lecithinase, lecithin is split into the water soluble haemolyticum lyso-lecithin and an unsaturated fatty acid which is adsorbed by the erythrocytes and which causes the change of their shape and a decreased aggregation.

The change of the sedimentation velocity of blood after storing at room temperature has been discussed by numerous authors, primarily because of its great practical interest. The determinations of the moment at which a noticeable change of the sinking reaction occurs vary considerably. *A. Westergren* (436) found in a series of 100 double determinations that storing for 4—5 hours was without any influence on the sinking reaction. First after 6—8 hours of storing, diverging results were obtained in rare cases. This interpretation was supported by *I. Freuchen*, 1925 (123), *M. D. Rourke* and *E. D. Plass*, 1929 (361), *M. Leffkowitz*, 1933 (250), *A. Eldahl*, 1934 (102), and *S. Frostad*, 1934 (139), while *K. Stöcklin*, 1926 (404), *M. Jersild*, 1934 (213), *L. Boström*, 1935 (42), *S. Christensen* and *S. A. Holboll*, 1937 (67), and *L. Koster*, 1937 (230), claimed that the blood sinking should be measured immediately after bleeding.

For a precise scientific investigation, the blood should therefore be as fresh as possible.

### *Ad III.*

The real sinking is superposed by the influence of thermal stabilization on the aggregation ability of the erythrocytes (and the viscosity of the plasma), (*J. Josefowicz*, 1922 (216)); if this effect is very marked, it may even noticeably modify the 1 hour-sinking (*K. Stöcklin* (404)). It is of greatest value for the scientific study of the sinking reaction to perform a microscopic control of the rouleaux formation and an estimation of the number

of non-aggregated, or weakly aggregated, thorn-apple shaped erythrocytes (*L. Boström*, 1935 (42), and 1940 (43)).

## § 15. THE EFFECT OF SHAKING ON BLOOD SINKING.

*E. Kaebisch* and *G. Simsch*, 1925 (218), observed that a blood sample which has been shaken with 1 or 1.5 hours intervals exhibits an unchanged sinking reaction. Even centrifuging followed by remixing does not influence the sinking reaction, as pointed out by *M. D. Rourke* and *E. D. Pla's* (361) and *M. Jersild* (213).

In shaken blood samples, *L. Berczeller* and *H. Wastl*, 1923 (27), constantly found an increased sinking in contrast to the expected reduced sinking. A decreased sinking, apparently after violent shaking, was observed by *H. Nasse*, 1836 (293).

*Berczeller* and *Wastl* (*loc. cit.*) report that the promoting effect of shaking was especially great in blood with a high aggregation tendency (horse blood). When investigating the sinking in vertically as well as obliquely arranged tubes during slow, continuous, non-intermitting streaming (in or out) of blood, *L. Berczeller* and *H. Wastl* (28) measured a vastly increased sinking. Using samples of horse blood in vertical tubes, the macroscopically visible erythrocyte aggregation occurred more quickly than in tubes with stagnant blood, thus indicating a manifest relation between this phenomenon and a conglomeration. When a rapidly flowing blood stream was suddenly stopped, the now motionless blood column showed a more rapid sedimentation than a blood sample which had not been in motion.

## § 16. ERYTHROCYTE STRUCTURE.

It is of little use to refer to the old dualism of whether the red blood corpuscles are built up like a balloon or like a sponge. In any case, these theories represent a far too naive idea of the complicated structure of this cell. (*Cf.*, among others, *E. Ponder*, 1934 (335)).

However, the surface properties of the erythrocytes are of the greatest significance for the aggregation problem. According to *H. Beumer* and *M. Bürger*, 1912 (32), *F. Haurowitz* and *J. Sladek*, 1928 (182), and *E. Jorpes*, 1932 (215), the erythrocyte membrane

consists of a lipoprotein; it is in agreement with this view that the cell surface of the erythrocytes at the interface between different media indicates rather hydrophobic properties (*S. Mudd and E. Mudd, 1931 (284)*). For the mentioned protein, the so-called "stromatin", *E. Jorpes (loc. cit.)* found a characteristic composition deviating from that of haemoglobin and plasma proteins. The stromatin content amounts to 4 per cent of the protein content of the erythrocytes.

*G. Boehm's* investigations, 1935 (38), revealed that stromatin consists of rod shaped micelles which form a membrane, and in the form of a gel, the stroma, fill the interior of the erythrocytes. Solutions of haemoglobin and salts are found in the meshes of this network. Optical investigations of the ultra structure of these membranes were carried out by *F. O. Schmidt, R. S. Bear and E. Ponder, 1936/37 (369)*, and 1938 (370).

## § 17. FACTORS DETERMINING THE SHAPE OF ERYTHROCYTES.

Since the disc form of the erythrocytes is a condition for the rouleaux formation as an orientated aggregation, the effect of different suspension fluids on the shape of the erythrocytes is of greatest interest. A number of substances cause a spherical erythrocyte form, others reproduce the disc form or maintain it. Altogether, these two groups of substances seem to promote or to suppress the aggregation, respectively.

The globular form is promoted by agents with a haemolytic effect, such as hypotonic dispersion media, saponins, salts of the bile acids, soaps, the thermal stabilizing lyso-lecithin, most of the lysines, bacteria lysines, and complement affecting sensitized erythrocytes (*E. Ponder (335)*; cf. also *F. Hinteregger (199)* discussed here on p. 29). If blood is exposed to a very high pressure (2000 atmospheres) the erythrocytes are transformed into spherocytes and, consequently, the blood sinking decreases (*U. Ebbecke, 1938 (87)*).

Wrinkling of the erythrocyte surface, *i. e.* thorn-apple shape, appears in hypotonic salt solutions and after storing of the blood (due to the thermal stabilization caused by a serum lipase, *B. Bergenhem and R. Fåhræus, 1936 (31)*). Skin fat, for example,



on dirty cover glasses, produces thorn-apple shaped erythrocytes (*G. Trönnberg*, 1939 (420) ).

Addition of lecithin to the plasma transforms the erythrocytes into spheres and inhibits rouleaux formation (*L. Lattes*, 1925 (244) ). Cholesterin (*J. Zozaya*, 1937 (458) ), various emulsoids as gelatin, gum arabic, tylose (*cf.* here, p. 166) which increase rouleaux formation preserve the disc form of the erythrocytes.\*) We find, thus, an antagonism between lecithin and cholesterin with respect to the form of the erythrocytes (*I. R. Brinkmann*, and *E. van Dam*, 1920 (47) ) and rouleaux formation (*H. Kürten* 1920 (237); *cf.* also p. 25).

In this connection, it should be mentioned that lecithin is a very strong emulsifier of oil in water, while cholesterin is an emulsifier of water in oil. At a certain ratio lecithin : cholesterin, a "phase-turn" occurs, *i. e.* a transition from oil in water to water in oil emulsions. However, this effect depends furthermore and to a high extent on the presence of salts and proteins (*cf.* primarily the review by *R. Degkwitz*, 1933 (81), and furthermore *H. Freundlich*, 1932 (125, Vol. II, p. 504) and *S. Palitzsch*, 1935 (321) ).

The surface forces can, however, hardly be considered the cause of the erythrocyte aggregations, the lipoids being of greatest influence on the electrical properties of the erythrocyte surface (*cf.* *R. Hirohata* and *H. Shimokawa*, 1935 (200), measurements of the cataphoretic velocity, and furthermore here, p. 41). The great influence of lecithin and cholesterin on the erythrocyte surface is illustrated by *E. Schiødt's* observations, 1931 (368, p. 72), concerning the permeability to ammonium bromide, which is increased or decreased, respectively, by addition of the mentioned substances.

## § 18. SPECIAL THEORIES OF ERYTHROCYTE AGGREGATION.

Since rouleaux formation has been known, numerous authors have made an attempt to give a theoretical interpretation of the phenomenon. In the main, all these theories are variations of

\*) *Addendum*: The publications by *R. F. Furchgott* and *E. Ponder*, *J. Exper. Biol.* 17, 30, 117, 1940, have not been accessible to the author.

the following four principles: stickiness, surface tension, electric charge, and hydration theories. These authors usually confined themselves to the assumption of one single determining factor and had no detailed conception of the aggregation mechanics.

The stickiness theory is the oldest aggregation theory (*H. Nasse*, 1836 (293), *F. Henle*, 1841 (187, p. 436), *J. Lister*, 1858 (263), and *Robin*, 1858 (355)). It was assumed that rouleaux formation is due to the stickiness of the erythrocyte surface or to a conglutination caused by the fibrin. With regard to the promoting effect of gum arabic on rouleaux formation, *H. Nasse* (*loc. cit.*) gave his opinion as follows "Gummi ersetzt also die Stelle des klebrigen Faserstoffs". Already *P. L. Panum*, 1851 (323), rejected *Henle's* stickiness theory and he was well aware of the ability of the fibrin to promote rouleaux formation. Also *Weber* and *Suchard*, 1880 (433), *E. Retterer*, 1906 (353), and *R. Fåhræus*, 1921 (109), rejected the stickiness as a decisive factor. In spite of *Fåhræus'* logical arguments against the primitive stickiness theory "If stickiness gave rise to the kind of agglutination here in question, the corpuscles would remain in the position of their first contact and we should not obtain the regular construction of the aggregates", this theory reappears at intervals (*G. Gruber*, 1924 (163), *E. Wöhlisch* and *P. Bohnen*, 1924 (453)), and even such authors as *E. Ponder*, 1926 (333), and *H. A. Abramson*, 1934 (5, p. 261), who had the greatest understanding of physico-chemical questions have not yet completely abandoned the stickiness theory.

The surface tension theory is almost as old as the stickiness theory (*R. Norris*, 1869 (298), *L. Ranvier*, 1875 (347)).

*Ranvier* regarded the aggregation process as a general phenomenon of suspended small particles.

*M. Heidenhain*, 1904 (184), who denoted as sympexis a conglomeration of suspended particles produced by capillary forces, argued (actually this argument does not hold) that colloids impede and crystalloids promote aggregation. He believed that the mouldability of the blood corpuscles was a necessary condition for their clustering together, since rouleaux formation failed to appear when the proteins of the erythrocytes were coagulated.

*E. Rothe*, 1924 (358), suggested, yet with a complete lack of

theoretical and experimental investigations, the consideration of the corpuscle and the surrounding plasma film as a unit. If these units were interpreted as drops of an emulgated substance it may be possible to speak of a surface tension of the corpuscles; thus, a high surface tension of the colloids of the protein film might favour the formation of large conglomerates. Similar theories have been outlined by numerous other authors (*Sachs, v. Oettingen, Kopaczewski, cf. the reviews on p. 6*).

*F. von Krüger, 1926 (236)*, made an attempt to decrease the boundary tension by adding milk or olive oil to the blood, but he did not find any change in the sinking reaction. In their attempts to reduce the surface tension of the blood by increasing amounts of sodium glycocholate, not even *A. Pines and M. Joffes, 1929 (330)*, were able to prove a relation between surface tension and sinking reaction.

Numerous authors (*Schemensky, v. Oettingen, Bechhold and Reiner, cf. p. 6*) assumed the existence of a relation between sinking reaction and excretion of surface-active substances, *i. e.* stalagmones in the urine. The stalagmone theory, however, was a purely speculative product.

*S. Mudd and E. Mudd, 1930/31 (284)*, tried to measure the interfacial tension between corpuscles and suspension fluid, this and not the surface tension of the fluid or the suspension at the interface air-liquid being the salient point in this question. On the basis of the observed "wetting properties" of the erythrocytes, the surface of the latter was considered relatively hydrophobic and non-polar. According to these authors, the corpuscle surface is built up of lipoproteins.

In general, *R. Höber, 1904 (203)*, and furthermore *G. Mangin and V. Henri, 1904 (270)*, are looked upon as the discoverers of the negative electric charge of the red blood corpuscles. However, already *Th. Jürgensen, 1860 (217)*, observed that frog corpuscles suspended in 0.5 per cent sodium chloride solution moved towards the anode when an electric field was supplied. Concentrated salt solutions inhibited or reduced the migration velocity. Similar to erythrocytes, most free cells are negatively charged relative to their natural suspension media. This is also the case with lymphocytes, bacteria, and spermatozoa (*R. Höber, 1926 (204)*).

After the discovery of the negative charge of the erythrocytes, the charge theory became the most important subject of discussion.

In Höber's laboratory, *R. Fåhræus*, 1918 (108), and *G. Linzenmeyer*, 1920 (258), determined the charge of the corpuscles by successive addition of lanthanum nitrate until the corpuscles ceased to move in the electric field. In this way, a relation between increased rate of sedimentation and reduced charge was found.

*T. Kanai*, 1922 (219), proved that globulin discharged better than albumin. *R. Mond*, 1922 (281), showed that ultraviolet irradiation of protein solutions changed the sinking velocity and the magnitude of the erythrocyte charge.

On the basis of these observations, *R. Höber* and *R. Mond*, 1922 (206), suggested the following theory. The electric charge of the blood corpuscles depends upon the ratio between globulin (isoelectric point  $p_H$  5.4) and albumin (isoelectric point  $p_H$  4.7) in the adsorption sheath. The stability of the suspension decreases in the presence of abundant amounts of globulin, and *vice versa*, since the tendency of globulin to form anions at the  $p_H$  of the blood is smaller than that of albumin. Consequently, just as in the case of suspensoids, the adjustment to the isoelectric point of the particles should cause maximum instability.

*R. Ley*'s experiments, 1922 (255), partly confirmed this theory. He found that horse corpuscles transferred into phosphate buffer of different  $p_H$  agglutinated at the highest or the lowest  $p_H$  after adsorption of fibrinogen or albumin, respectively. *J. Northrop* and *P. de Kruif*, 1922 (299), made similar observations upon bacteria.

However, numerous papers appeared bringing forward results which made the correctness of the charge theory rather doubtful. Earlier supporters, for example *R. Fåhræus* (109), renounced this theory in favour of a hydration theory (*cf.* later). *G. Linzenmeyer* (260) mentioned that gelatin promotes the sinking without reducing the electric charge of the corpuscles and, as a consequence of this discovery, he could no longer consider the erythrocyte charge decisive (258).

In the course of time, the electrophoretic determinations played a greater part in the study of the surface properties of the blood corpuscles, especially with regard to the decision of

the principal problems of the charge theory, *viz.* of whether the plasma colloids are adsorbed by the erythrocytes, and the extent to which aggregation is accompanied by a reduced charge of the erythrocytes.

*H. Netter*, 1925 (294), noticed that horse corpuscles which form less stable suspensions than ox corpuscles have a higher electrokinetic potential.

*M. Schechter* and *Th. Blühbaum*, 1927 (367), found an almost constant cataphoretic migration velocity of the corpuscles of blood with different sinking velocity (*cf.* below, *H. A. Abramson*, 1929 (3) ); blood to which varying amounts of lanthanum nitrate were added did not show varying sinking reactions.

A detailed investigation of the erythrocyte cataphoresis in different media was carried out by *H. A. Abramson*, 1934 (5). *H. A. Abramson* (3) was furthermore able to demonstrate a great difference in the cataphoretic velocity of the erythrocytes of different animals (at  $p_H$  7.35 in a M/15 phosphate buffer) and he outlined a decreasing series, the extremes of which are represented by dogs and rabbits, respectively. A similar succession was found later by *H. L. White* and *B. Monaghan*, 1936 (443). (*Cf.* furthermore, Table 2, p. 42).

The blood corpuscles of new-born children, adults, pregnant, and patients suffering from various types of anaemia showed almost the same cataphoretic velocity. In spite of the considerable inequality of the size of anaemia corpuscles, of their shape, and their haemoglobin content, these corpuscles moved with approximately the same velocity. Although rabbit corpuscles are  $7.16 \mu$  in diameter, and dog corpuscles are  $7.20 \mu$  in diameter, the first mentioned migrated slowest and the latter quickest of the erythrocytes of all species investigated, thus indicating the lack of any relation between size and migration velocity. The migration velocity was independent of whether the corpuscles moved with one or the other orientation; rouleaux moved with the same velocity as single blood corpuscles, *i. e.* the aggregation was not accompanied by a change of the electrokinetic potential of the corpuscles (*H. Freundlich* and *H. A. Abramson*, 1927 (126), and *H. A. Abramson* (5) ).

Hence, the independence of the cataphoretic velocity on

shape and size of the particles accords with the *Helmholtz-Smoluchowski* theory (385), where

$$v = \frac{\zeta H D}{4 \pi \eta} \quad (3)$$

( $v$  is the migration velocity,  $\zeta$  the electrokinetic potential,  $H$  the outer drop of potential,  $D$  the dielectric constant, and  $\eta$  the coefficient of internal friction of the suspension medium). In contrast to this, *P. Debye* and *E. Hückel*, 1924 (79) and (80), derived that this formula holds only in the case of cylindrical particles, while spherical particles claim the factor 6 instead of 4. A discussion of this problem may be found in *D. C. Henry's* paper, 1931 (190), (*cf.* furthermore p. 60 of the present paper). *H. Müller*, 1933 (290), gave a critical survey of *Henry's* theory (*loc. cit.*). In comparative investigations, however, the discussed problem may be disregarded.

As a criterion for the formation of an adsorption layer on the erythrocyte surface, *R. Höber* and co-workers pointed out that the isoelectric point of the corpuscles corresponds to that of one of the plasma proteins. *R. Ley's* investigations (255) were already mentioned before in connection with the *Höber-Mond* theory. On the basis of measurements of the isoelectric point, *H. Netter* (294) emphasized that the slowly sedimenting ox corpuscles adsorb albumin, while the adsorbing layer of the rapidly sinking horse corpuscles mainly contains globulin. Nevertheless, *Netter* observed that horse corpuscles had a higher electrokinetic potential than ox corpuscles (at  $p_H$  7.8—8.0).

*S. Kozawa*, 1914 (231), found that addition of a suitable amount of acid brought the blood corpuscles to the isoelectric point (cataphoretic velocity = 0) which was characteristic of the respective species investigated. However, the amount of acid was not constant but dependent on the time of action. Also *C. B. Coulter*, 1920 (70), *A. H. Eggerth*, 1924 (91), and *H. Netter*, 1925 (294), noticed that the isoelectric point of human, rabbit, and horse blood corpuscles varied with the time of measurement. According to *H. A. Abramson*, (5, p. 261), it is almost impossible to determine the isoelectric point of intact erythrocytes because their surface is changed very rapidly in a medium with

low  $p_H$ . The inaccurate determinations of the isoelectric point (Coulter, Eggerth, Netter, and others) are due to protein adsorption to injured cells (H. A. Abramson (4)). The same author (3) found that "ghosts" show the same cataphoretic migration velocity as whole erythrocytes in a buffered isotonic solution. This observation was confirmed by W. H. Byler and H. M. Rozendaal, 1939 (62), and by H. A. Abramson, R. F. Furchgott and E. Ponder, 1939 (6). H. L. White and B. Monaghan, 1936 (443), determined the isoelectric point of such ghosts instead of the whole red cells.

A serious argument against the assumption of the protein adsorption to the corpuscles is the low isoelectric point of normal erythrocytes ( $p_H \cong 3$ ) relative to that of plasma proteins (H. A. Abramson, 1931 (4), H. L. White and B. Monaghan (443)). Abramson, who was the first to furnish a proof against the protein adsorption, demonstrated (3) that repeated washing of the erythrocytes did not change the cataphoretic velocity, thus indicating a lacking, or at least a (by washing) not removable adsorption layer. The same author found, moreover, (1931 (4)), that red blood corpuscles suspended in dilute serum at any  $p_H$  (above 3.5) never showed the same mobility as quartz particles suspended in the same medium.

In a number of cases, J. G. Stephens, 1938 (395), observed a separation into layers of the blood column during sinking, appearing as one or a few diffuse, light layers above the compact blood column (cf. sinking with diffuse boundary, "Schleiersenkung", p. 21) forming an expression of a flotation of unripe cells with a low aggregability. The cataphoretic velocity of the erythrocytes increased with every layer beginning from the top layer, here amounting to 1/2 or 2/3 of the normal cataphoretic migration velocity ( $1.86 \mu/\text{sec}/\text{volts}/\text{cm}$  at  $p_H = 7.4$  in an isotonic glucose solution with buffer).

Stephens explained the reduced aggregation tendency in spite of the reduced potential as a change in the erythrocyte surface. Furthermore, the unripe cells are of a more spherical shape than normal erythrocytes. In cases of icterus haemolyticus in man, after splenectomy, and in dog foetes, J. G. Stephens, 1938 (394), detected erythrocytes with a decreased aggregability and a cataphoretic velocity of only 2/3 of the normal. According to

some older and especially a number of recent investigations, however, the increased aggregation tendency seems to be connected with an increased electrokinetic potential, in contradistinction to the interpretation of Höber's school. Primarily, *H. L. White* and *B. Monaghan* (443) drew our attention towards this point, although these authors agree with *R. Fåhræus*' hydration theory (cf. below p. 43).

*E. Ponder* (333) reported a marked aggregation of erythrocytes in spite of a high potential, but he denied the influence of charge on this effect. However, he argued that a high electrokinetic potential is the cause of the aggregation to rouleaux formation, since only a decrease in potential makes irregular conglomerates possible.

*R. Hirohata* and *H. Shimokawa* (200) realized that the cataphoretic velocity of the erythrocytes in their own plasma(!) is increased during pregnancy, acute infections, tubercular diseases and cancer, and sometimes even reaches twice the value found in normal healthy persons. The cataphoretic velocity is decreased by addition to the blood of neutral fat and lecithin, and it is increased by cholesterol and cholesterol ester. The erythrocytes showed a higher cataphoretic velocity in solutions containing fibrinogen and pseudo-globulin than in solutions of euglobulin and albumin. The migration velocity of erythrocytes in their own plasma was sometimes found to be parallel with the sinking reaction, and sometimes not.

In a comparison of the cataphoretic velocity in different media it is necessary to take the viscosity into account, especially when dealing with solutions of emulsoids. This fact has been discussed by numerous investigators (*E. Ponder* (333), *H. A. Abramson* (5, p. 169), and *B. Monaghan* and *H. L. White* (280)); however, the present author is unaware of whether *R. Hirohata* and *H. Shimokawa* paid due regard to it.

*H. L. White* and *B. Monaghan* (*loc. cit.*) and also *A. H. Abramson* (*loc. cit.*) found an increasing erythrocyte cataphoretic velocity in different animal species, the erythrocyte aggregability increasing with increasing electrokinetic potential. The tendency to aggregation was measured as a sedimentation in an "artificial" plasma consisting of 1 per cent gelatin dissolved in 0.9 per cent sodium chloride solution which was brought to  $p_H$  7.4 by means



of N/50 phosphate buffer (cf. Table 2). This observation is in good agreement with *J. de Corral* and *I. Villalonga's* classification of the erythrocytes of different species, (1932 (68), in rapidly and slowly sinking erythrocytes (cf. p. 11)). *H. A. Abramson* (3), and *M. Schechter* and *Th. Blihbbaum* (367) measured a constant cataphoretic velocity (in the same medium at constant  $p_H$ ) of erythrocytes of blood with different sinking velocity (the same species of animals and man), which indicates the same surface properties and the same aggregation tendency of the erythrocytes. This result confirms *R. Fåhræus'* view (109) that the plasma properties are the dominating factor for the aggregation within the same species.

Table 2.

(According to *B. Bergenhem*, 1938 (30), slightly modified.)

Animal species	Sinking velocity of the blood corpuscles		Cataphoretic velocity $\mu$ /sec./volt/cm. at $p_H$ 7.4 according to		Isoelectric point $pI$ of erythrocyte stromata (White and Monaghan)	Erythrocyte cholesterol % (Swedin)
	in artificial plasma (White and Monaghan)	in own plasma (Swedin)	White and Monaghan	Abramson		
Dog ..	122 mm/20	0.2 mm/2 hs.	1.59	1.65	2.7	2.44
Horse.	111 min.	120 mm/1 h.	1.56			1.58
Man ..	94	2-9 mm/1 h.	1.34	1.31		1.66
Cat ...	57		1.34	1.39		
Rat ...	46		1.31	1.45		
Pig ...	36		1.02	0.98		
Ox....	2	0-4mm/24hs.	0.98		3.4	1.74
Rabbit	0	0.5 mm/1 h.	0.47	0.55	4.3	1.17

*Riho Hazama*, 1937 (183), measured the cataphoretic migration velocity of red blood corpuscles in their own plasma and he was able to prove that these measurements are of the same clinical significance as the corresponding determination of the sinking reaction. In other words, also here the electrokinetic potential varies symbatically with the total aggregability which is determined partly by the erythrocytes and partly by the medium.

Due to imperfections in the earlier applied technique (discharge by means of lanthanum nitrate (108)), *R. Fåhræus*,

(109, p. 147), abandoned the charge theory and assumed that the hydrophilic plasma colloids deprive the corpuscle surfaces of adsorbed water, thus causing a decrease in the suspension stability. According to *R. Fåhræus* (110), this is in agreement with the promoting effect of different emulsoids (gelatin, casein, gum arabic) upon the aggregation. The assumption of the corpuscle hydration was based upon the fact that the corpuscles are of the greatest influence upon the blood viscosity. Herewith the era of the hydration theory is initiated.

In this connection, we shall remind of *R. Hirohata* and *H. Shimokawa's* experiments (200) and further experiments by *B. Monaghan* and *H. L. White* (280) who found an increased electrokinetic potential when the aggregability was increased by addition of emulsoids. When looking at Table III of the last mentioned paper (*loc. cit.*) we find the already discussed sequence of the cataphoretic velocity of erythrocytes of different species, even after addition of emulsoids to the buffer solution. The corrected migration velocity and the sinking reaction increased with increasing concentration of the respective emulsoids.

In 1929, *R. Fåhræus* (3) formulated the principal problem of rouleaux formation as follows. "The problem seems to hinge upon the manner in which the globulin increase changes the interface between the corpuscles and the plasma or, let us say, the surface of the red cells. Is it by increasing the surface tension, or by reducing the negative electric charge of the corpuscles or finally by depriving their surface colloids of adsorbed water?"

In contrast to *J. Oliver* and *L. Barnard's* interpretation, 1924 (311), of blood corpuscle suspensions as hydrophobic colloids, *W. M. Bendien*, *J. Neuberg* and *I. Snapper* (21) felt forced to abandon the critical potential theory, since the erythrocyte aggregation is due to a mutual coagulation of colloids, a so-called "sensibilization". The lability of the plasma proteins which is decisive in this case does not directly depend on the electric charge, but also on the hydration.

In the repeatedly mentioned, very significant papers by *H. L. White* and *B. Monaghan* (280 and 443), great stress is laid upon the essential influence of the surface hydration upon the aggregation, while the electric charge is considered to be of secondary importance in spite of the parallelism between aggregation and

electric charge. This view is supported by observations concerning the position of the isoelectric point of the erythrocytes and the change of their cataphoretic migration velocity after addition of hydrophilic colloids (gelatin, casein, albumin, and fibrinogen). If the corpuscles were not hydrated, an increase in the colloid concentration should cause a considerably greater decrease in the electrophoretic mobility of the corpuscles than the plasma proteins. If this is not the case, *i. e.* if the cataphoretic velocity decreases but slightly or even not at all with increasing colloid concentration, we must assume that the viscosity in the electric double layer of the erythrocytes is already high due to the orientated water molecules. In agreement with *Fåhræus*, *White* and *Monaghan* emphasize: the thinner the orientated water film, the greater the surface energy of the boundary layers; consequently, the aggregation must be produced by the dehydration of the corpuscle surface through the colloids. However, albumin did not cause aggregation, in contrast to casein, fibrinogen, and gelatin (*cf. R. Hirohata and H. Shimokawa's* experiment described on p. 41).

The different cholesterin and lecithin content of the erythrocytes of different species has also been brought into relation to the varying aggregability; the greater the lipid content, the easier dehydration and aggregation. According to *H. L. White* and *B. Monaghan* (443), the low isoelectric points of cholesterin and lecithin ( $pI = 2.2$  and  $3.2$ , respectively) cause a high cataphoretic velocity of the erythrocytes at the blood  $p_H$  when the lipid content of the erythrocytes is high (*cf. R. Hirohata and H. Shimokawa*, p. 41). This is in rather good agreement with *B. Swedin's* determination of the cholesterin content of the blood corpuscles (406); (*cf. Table 2*, p. 42).

## § 19. MEASUREMENT OF THE SEDIMENTATION VELOCITY AND THE SHAPE OF THE SINKING REACTION CURVE.

In order to render the rate of blood sinking amenable to observation over a longer period of time, the blood must be prevented from coagulating. Since, however, all substances which inhibit coagulation (citrate, oxalate, hirudin, heparin, and so on) cause a change in the blood sedimentation, it is actually impossible

to observe the "natural" sinking and we must confine ourselves to the measurement of a well-defined artificial process.

For the application to macromethods, the blood is gained by a vein puncture (after short stasis) and an accurately measured amount of citrate is added (for instance, by sucking it up in advance into a record syringe). *Linzenmeyer* used 5 per cent, *Westergren* 3.8 per cent citrate, and a ratio blood : citrate = 4 : 1 (*cf.* the effect of electrolytes, pp. 16 and 22). After careful mixing of the blood, the sinking tube is filled immediately and is placed vertically.

In general, *A. Westergren's* technique, 1924 (436), has been employed, but a method described by *G. Linzenmeyer*, 1920 (259), 1922 (261), and 1923 (262), has also numerous supporters. *Linzenmeyer* determines the moment when a certain plasma level is reached (mark at 18 mm, length of the blood column 50 mm, the tube is closed at the top, 70 mm long, 5 mm in diameter). *Westergren* determines the height of the plasma level at given moments (mm, after the lapse of 1, 2, and 24 hours; height of the blood column 200 mm, tube open at the top, length 300 mm, diameter 2.5 mm). For further details regarding the technique of measuring blood sinking, *cf.* the surveys p. 6.

When speaking in the present paper of the sinking reaction in general, *Westergren's* 1 hour value is always kept in mind. The author's own technique is described on p. 154.

In order to obtain a more complete picture of the sinking reaction convenient for scientific investigations, readings may be taken at small time intervals (*Fåhræus*, *Westergren*, and many others). Plotting corresponding values of the height of the plasma level and the time from beginning sedimentation in a coordinate system leads to the curve of the sinking reaction. Finally, photographic registration makes a direct observation of the sinking reaction possible (*G. Gollnow*, 1932 (152), *F. Frimberger*, 1933 (136), and many others; *cf.* also *H. Reichel*, 1936 (351)).

By means of *Westergren's* technique we obtain an S-shaped curve of the blood sinking. The shape of the curve has been discussed by *R. Fåhræus* (109), *A. Westergren* (436), *E. Rothe*, 1924 (358), *R. Lundgren*, 1927 (266), and *B. Swedin* (407).

According to *Rothe (loc. cit.)*, three regions may be differentiated,

- 1) "pre-agglutination sinking", including the first bend of the curve;
- 2) "agglutination sinking", represented by the linear part of the curve, and
- 3) "sacking" ("Sackung"), the last bend of the curve which is caused by a "packing effect".

The course of the sinking reaction curve clearly demonstrates the predominant influence of the aggregation on the blood sinking, *viz.* a rapid sinking during strong aggregation and a slow sinking during slight aggregation, as already emphasized by R. Fåhræus (109).

As time of aggregation, R. Fåhræus denoted that space of time which passes until the aggregates attain their maximum size, corresponding to the linear part of the curve. Neither Fåhræus nor Lundgren defined the limits of this time of aggregation; according to S. Odén, 1920 (303), it seems reasonable to use the point of intersection of the linear part of the curve with the axis of abscissae, the latter thus indicating the time, and the axis of ordinates representing the route already passed. The time of aggregation which is a measure of the aggregation velocity varies from one to a few hours in the case of slowly sedimenting blood, down to a few minutes in cases of very rapid sinking reactions. During the time of aggregation, the erythrocytes sink only very slowly. One of B. Swedin's sedimentation experiments (407) carried out in Theorell's cataphoresis apparatus (blood sample with a sinking of 24 mm/hour; column of 60 mm, which was separated in 6 equal volumes after the lapse of 5 min.) indicated no verifiable decrease in concentration (determined by haematocrite in the upper layers of the suspension during the first phase of the sedimentation).

Fåhræus found furthermore, apart from the dominating influence of the growth of the aggregates, a secondary cause of the increased sedimentation velocity of the conglomerates, *viz.* an increasing density due to a — more or less complete — pressing out of the plasma in the interspaces of the aggregates.

The shape of the sinking reaction curve reveals that sinking occurs very slowly until the aggregates have attained a certain size. As soon as the linear part of the curve begins, the conglomerates have reached their final size and density, which are not

increased during this phase of the sedimentation process (*cf.* later, p. 163). During maximum sinking, the cessation of the aggregation is presumably produced by the almost uniform size of the aggregates and the rising stream of plasma. When the aggregates reach so far that their velocity decreases on account of the packing effect a continuation of the aggregation becomes possible.

*H. Gessner's* interpretation of the S-formed sinking reaction curve, 1931 (151), as an expression of a sedimentation with "orthokinetic" coagulation will be discussed on p. 168.

Numerous investigators, as for example *R. Lundgren* (266) and *B. Swedin* (407), realized that the ordinary single reading (*Westergren's* 1 hour value) does not reveal the true sedimentation velocity. The actual rate of sedimentation can only be read in the linear part of the sinking reaction curve. In the other regions of the complicated curve, the sedimentation velocity is determined by the tangent of the curve (or the first differential quotient of the function describing the curve). On the basis of his tangent method, *R. Lundgren* (*loc. cit.*) suggested the measurement of the sinking reaction by that sinking per hour which the blood would reach at the maximum sinking velocity, corresponding to the linear part of the curve.

In a later discussion, *Westergren* stated (cited from *Swedin* (407)) that he had made an attempt to apply the tangent method; however, he objected that the tangent was difficult to measure. In the meantime, this difficulty seems to be surmounted by means of a modification of *Swedin's* apparatus (*cf.* below, p. 48). The tangent method offers some idea of the extent of aggregation; the sedimentation velocity which is proportional to the size of the aggregates moreover depends upon the viscosity of the whole suspension. *Lundgren* did not find any certain relation between the 1 hour sinking and the maximum sinking determined by the tangent method. In other words, the time of aggregation may vary independently of the size of the aggregates, corresponding to the linear part of the curve. By means of a trick — presumably mechanical influence such as shaking — which until now has been reserved for later publication, *Lundgren* varied the time of aggregation without changing the slope of the linear part of the curve.

The moment of appearance of the "sacking phase" depends on the height of the blood column and on the volume concentration of the erythrocytes. The packing begins the earlier, the shorter the blood column and the greater the volume of the erythrocytes. This fact is of greatest significance for the practical performance of the sinking reaction, where it is important to avoid readings in the badly defined and hardly estimable phase III. The packing of the corpuscles, which inhibits the sinking reaction, may be avoided in *Swedin's* modification of the apparatus (407) in which the upper end of the sedimentation tube is closed by means of a cock and the tube is immersed into a test-tube containing blood. Using this arrangement, the sinking curve becomes completely linear as soon as phase I has been passed.

In *Westergren's* generally applied blood sinking technique, the blood column is 200 mm high, these long tubes being of great advantage with respect to the accuracy of the readings. At an erythrocyte volume concentration of 0.5, the maximum sinking measured in columns of 200 mm and 50 mm is 100 and 25 mm, respectively. A simple conversion from one height of the column to another is not permissible, since the beginning of the sacking phase depends not only upon the height of the column but furthermore on the volume of the blood corpuscles.

The influence of the tube diameter on the course of the sinking reaction has been studied by *P. Wiemer*, 1927 (450). (For further literature, cf. *H. Reichel*, 1936 (351)). Narrow tubes (often applied in difficult and ambiguous micromethods) have sometimes a promoting and sometimes an inhibiting effect on the sinking reaction, markedly dependent on the aggregation properties of the individual blood sample (such as coarse, large agglutinates in non-anaemic blood, etc.). Above certain dimensions of about 1.5 mm, the diameter of the tube seems to be without any influence on the blood sinking. *Westergren's* tube is 2.5 mm in diameter.

The method of filling the tubes may also have some influence on the results. If the wall of the tube was wetted above the column during filling — like a test-tube filled from above (*Linzenmeyer* tube) — an increased sinking reaction has been observed, presumably due to rapidly formed aggregates in the blood flowing down along the wall. This may be avoided by sucking the

blood into the tube — similar to the filling of a pipette (*Westgren's tube*) (*H. Reichel, loc. cit.*).

Also the rate of flow of the blood during filling of the sinking pipette may affect the results (*L. Berczeller and H. Wastl, 1924 (28), cf. below, pp. 32 and 190*).

An inclination of the vertical sinking tube of only  $5^{\circ}$  already produced a marked increase in the sinking reaction. Due to the relatively short sedimentation path in an inclined tube, the aggregates accumulated rapidly and grew like avalanches along the lower wall of the tube, while the plasma stream escaped at the top.



## Section II.

### COLLOID PHYSICS.

#### § 20. COLLOID STABILITY. STOKES' FORMULA.

The dispersion degree of a colloidal solution — the decisive factor for numerous essential properties — is the statistical result of two antagonistic processes, *viz.* dispersion and condensation (*i. e.* peptization, increase in the number of particles, or decrease in their size and, on the other hand, flocculation, coagulation, decrease in the number of particles, or increase in their size). These processes are characteristic of colloid chemistry.

If the particles of the colloidal solution were at complete rest and not affected by any forces maximum stability would be attained and the durability of the system would be infinitely long. However, the dispersed particles are affected by various forces, primarily by the gravity which — proportional to the difference between the specific gravity of the particles and that of the suspension fluid — tends to move the particles upwards or downwards (sedimentation) and thus to disturb the system.

Within certain limits, *Stokes'* classical formula holds for the velocity of falling of a spherical particle (*G. G. Stokes*, 1845 (401) and 1851 (402), *H. Lamb*, 1916 (242), *C. W. Oseen*, 1927 (317), and *H. Gessner*, 1931 (151)). In the case of a laminar flow around the sphere, the resistance may be described by the formula

$$W = (6\pi\eta r) v, \quad (3)$$

where  $r$  is the radius of the sphere,  $v$  its velocity, and  $\eta$  the internal friction of the suspension fluid. When the sphere is affected by an accelerating force, as for example by gravity, it will finally obtain a constant velocity. The resistance to motion is then equal to the moving force.

The sedimentation velocity  $v$  of a spherical particle or aggregate with radius  $r$ , density  $D$ , suspended in a fluid of density  $d$  and

internal friction  $\eta$  becomes thus

$$v = \frac{\text{force}}{\text{resistance}} = \frac{\frac{4}{3} \pi r^3 (D-d) g}{6 \pi \eta r} = \frac{2 (D-d) g}{9 \eta} = Cr^2, \quad (4)$$

where  $g$  is the acceleration due to gravity, and  $C$  is a constant.

If coagulation occurs in this colloidal system, the sedimentation velocity is rapidly increased due to the increasing radius of the particles, so that a precipitation takes place.

Since coagulation is conditioned by collisions of particles, repulsive and attractive intercorpuseular forces — counteracting or promoting the collisions produced by Brownian movements — have great influence upon the stability of the system. This is a corroboration of the true coagulation theory.

A number of authors, among whom we find *H. S. Allen*, 1900 (16), *C. W. Oseen*, 1910 (314) and 1913 (316), *H. D. Arnold*, 1911 (17), *A. Westgren*, 1914 (438), and *J. Nordlund*, 1918 (297), investigated experimentally the validity of the sedimentation formula.

A number of conditions must be fulfilled in order that *Stokes'* formula applies, *viz.*

- 1) The particle must be smooth, rigid, and spherical.
- 2) No sliding is allowed to occur between the medium and the particle.
- 3) The particle must be large compared with the mean free path of the molecules of the suspension fluid.
- 4) The velocity of the particle should not exceed a given critical value, *i. e.* its radius must not be too great.
- 5) The constant velocity of falling must be attained.
- 6) Compared with the dimensions of the particle, those of the medium must be infinite.

*Ad 1).*

In the case of blood corpuscles and their aggregates which may be regarded as smooth, but neither as rigid nor as spherical, it is necessary in analogy to dispersoid analysis to introduce *S. Odén's* "equivalent radius" (302). The equivalent radius of a particle is defined as the radius of the ideal sphere whose velocity of falling corresponds to that of the observed particle. Using *Stokes'* formula, we get

$$r = \sqrt{\frac{v}{C}} = \sqrt{\frac{9\eta v}{2(D-d)g}} \quad (5)$$

Due to the Brownian movement, a small, non-spherical particle will change its orientation in the direction of the fall so that the hydrodynamic resistance changes. If the measurement of a single particle's sedimentation velocity is replaced by the measurement of the mean velocity of all particles, the equivalent radius calculated from the shape of the particle will agree satisfactorily with that derived from the mean velocity. Calculations and measurements were performed by *A. D. Hall*, 1904 (172), and *E. J. Russell*, 1932 (363). Furthermore, *J. Boselli*, 1911 (41), measured the sedimentation velocity of the corpuscles of various animal species, and *R. Fåhræus* (109, p. 111) determined the sedimentation velocity of human corpuscles.

With the equivalent radius, however, the true dimensions of the micelles are not yet described, since the velocity of falling moreover depends on the specific gravity which may vary with the aggregation as well as on account of the hydration of the particles. In the case of corpuscle conglomerates, for example, the equivalent radius can decrease even if the true radius increases, since some of the lighter plasma is enclosed between the heavier blood corpuscles during aggregation, and the sedimentation velocity is thus reduced.

*Ad 2), 3), 4), and 5).*

These conditions may be considered fulfilled in the case of blood corpuscles. The minute space of time until the velocity of falling becomes constant may be disregarded (*cf. H. Gessner*, 1931 (151, Table 1, p. 14)).

*Ad 6).*

This condition is not fulfilled in the case of blood corpuscle suspensions, due partly to the mutual friction between the particles and their intercorpuscular forces, partly to the walls of the tube.

*E. Cunningham*, 1910 (72), was able to prove that *Stokes'* law is valid also in concentrated suspensions if a friction coefficient is introduced which varies with the concentration of the particles. In the case of very dilute suspensions, *Stokes'* law always holds (*S. Odén*, 1932 (305)).

## § 21. THE INFLUENCE OF THE WALLS OF THE VESSELS ON THE MOVEMENT OF THE PARTICLES.

With regard to a later application to the movement of particles between plano-parallel walls (p. 170), the formulas which describe the influence of the walls will be discussed in detail.

*H. Faxén*, 1921 (114), has given a generally valid formula

$$W = \frac{6 \pi \eta r v}{1 - \frac{3}{4} \sigma r - \frac{9}{16} \frac{r}{l} \chi(\sigma l)}, \quad (6)$$

where  $\sigma = \frac{dv}{2\eta}$ ,  $l$  being the distance between the centre of the sphere and the wall,  $\chi(\sigma l)$  a complicated function of  $(\sigma l)$ , and all other terms being the same as in the preceding formulas. It follows from this formula that the influence of a plane vertical wall on the velocity of a falling sphere is a function of the so-called *Reynold's* number  $(\sigma l)$ .

When *Reynold's* number is very high (above 5), *Faxén's* formula is transformed into *C. W. Oseen's* resistance formula (317) which no longer shows the influence of the surrounding walls,

$$W = \frac{6 \pi \eta r v}{1 - \frac{3}{4} \sigma r}. \quad (7)$$

*Oseen's* resistance formula holds at higher velocities of falling or at greater radii of the particles, respectively, than in *Stokes' formula*, the validity of which fails at a radius of about  $100 \mu$ .

If *Reynold's* number is small, *Faxén's* formula gets the form of the *H. A. Lorentz's* expression, 1906 (264),

$$W = \frac{6 \pi \eta r v}{1 - \frac{9}{16} \frac{r}{l}}. \quad (8)$$

If we assume, in agreement with *A. Westgren*, 1918/19 (441), the distance ( $l$ ) of the particle from each of the walls of a plano-parallel cuvette to be equally probable, and furthermore, *Lorentz's* formula to be valid, we get the mean resistance  $W_m$

$$W_m = \frac{6\pi\eta rv}{L-r} \int_r^L \left(1 + \frac{9}{16} \frac{r}{l}\right) dl = 6\pi\eta rv \left[1 + \frac{9r}{16(L-r)} \ln \frac{L}{r}\right], \quad (9)$$

where  $2L$  is the distance between the walls.

By means of this formula, a correction for the influence of the walls upon the movement of the particle parallel to the walls may be calculated; either the movement of the particle is due to an external force, or to the Brownian movement derived in terms of the diffusion constant

$$\text{Diffusion constant} = \frac{H\Theta}{N} \frac{1}{6\pi\eta r \left[1 + \frac{9r}{16(L-r)} \ln \frac{L}{r}\right]}, \quad (10)$$

where  $H$  is the gas constant,  $\Theta$  the absolute temperature, and  $N$  Avogadro's number.

Westgren (439) emphasized, however, that the formula for the resistance is scarcely compatible with the formula found experimentally by himself, viz

$$W = 6\pi\eta rv \left(1 + 3.4 \frac{r^2}{L^2}\right). \quad (11)$$

## § 22. THE BROWNIAN MOVEMENT OF COLLOIDAL PARTICLES. HYDRODYNAMIC PROBLEMS CONCERNING THE MOVEMENT OF NON-SPHERICAL PARTICLES.

The Brownian movement of colloidal particles is of fundamental importance as a carrier of dispersion and aggregation which are the colloido-physical elementary processes.

From the view-point of molecular kinetics which proved to be especially productive in the elucidation of coagulation problems, the theory of the Brownian movement was developed by A. Einstein, 1905/22 (95—99), and by M. v. Smoluchowski, 1906 (383) and 1923 (388). The first proofs of the validity of the theory and, hence, of the molecule concept were furnished by T. Svedberg, 1912 (405), and J. Perrin, 1936 (327). A historical survey of the theories of the Brownian molecular movement may be found in G. de Haas-Lorentz' brilliant monography, 1913 (170).

A. *Einstein* (95) assumed that the colloidal particles (due to their Brownian movement) exert the same pressure on a semi-permeable wall as the corresponding number of dissolved molecules; on this assumption, *Van't Hoff's* law  $p = cH\Theta$  got a new meaning ( $p$  = osmotic pressure,  $c$  = the concentration in mols per litre of the dissolved substance,  $H$  = the gas constant, and  $\Theta$  = the absolute temperature). This interpretation of the colloidal particle as a molecular-kinetic unit is also the basis of *M. v. Smoluchowski's* theory (383) that the particles behave as independent gas molecules with a normal kinetic energy, but with a very small mean free path.

*Einstein's* theory is based upon *Maxwell-Boltzmann's* theorem according to which the mean energy is equally distributed between the state parameters of a system in thermodynamical equilibrium.

The mean square of the fluctuations of the state parameter  $\Delta$  in the course of time  $t$  was calculated by *Einstein* (97) as follows

$$\overline{\Delta^2} = 2 \frac{H\Theta}{N} Bt, \quad (12)$$

where  $H$  is the gas constant,  $N$  *Avogadro's* number,  $\Theta$  the absolute temperature, and  $B$  the mobility of the system according to the state parameter.

The mean square of the displacement of the suspended sphere in the direction of the  $x$ -axis is

$$\overline{x^2} = 2 \frac{H\Theta}{N} \frac{1}{6\pi\eta r} t \quad \text{since } B = \frac{1}{6\pi\eta r}. \quad (13)$$

Correspondingly, the mean square of the rotation displacement of a sphere  $\Delta_r$  in the time interval  $t$  becomes

$$\overline{\Delta_r^2} = 2 \frac{H\Theta}{N} \frac{1}{8\pi\eta r^3} t, \quad \text{where the mobility } B = \frac{1}{8\pi\eta r^3}. \quad (14)$$

As is evident from the formulas, with increasing radius of the particle the rotation movement decreases more rapidly than the translational movement.

If the displacement of the particle in the direction of the  $x$ -axis is expressed by means of the diffusion coefficient,

$$D = \frac{H\Theta}{N} \frac{1}{6\pi\eta r} \quad \text{we get } \overline{x^2} = 2Dt. \quad (15)$$

The mean square of the displacement in a plane or in space is

$$\overline{x^2} = \overline{y^2} = \overline{z^2} = 2Dt; \quad \begin{aligned} \overline{x^2} + \overline{y^2} &= 4Dt, \\ \overline{x^2} + \overline{y^2} + \overline{z^2} &= 6Dt, \end{aligned} \quad (16)$$

according to the rules of addition of the independent square errors.

With regard to the Brownian movement of non-spherical particles and their movement due to external forces, it seems necessary to discuss some hydrodynamics. The particles (erythrocytes) which move in a viscous fluid (the plasma) are regarded as oblate ellipsoids of revolution.

The fundamental hydrodynamic equations may be employed in *G. G. Stokes'* approximative form if the movements are sufficiently slow (*H. Lamb*, 1916 (242)). By integration of these equations, *A. Oberbeck*, 1876 (300), obtained the friction coefficients of the translational movement of ellipsoids, and *D. Edwardes*, 1892 (88), found the friction coefficients of the rotation of ellipsoids.

We confine ourselves to the discussion of oblate ellipsoids of revolution. If  $a$  denotes the half length of the axis of symmetry and  $b = c$  the lengths of both other semi-axes, where  $a < b = c$ , and  $A$ ,  $B$ ,  $C$ , and  $S$  be the elliptic integrals,

$$A = \int_0^\infty \frac{ds}{(a^2 + s)(b^2 + s)\sqrt{a^2 + s}} = \frac{1}{a^2 - b^2} \left( S - \frac{2}{a} \right), \quad (17)$$

$$B = C = \int_0^\infty \frac{ds}{(b^2 + s)^2 \sqrt{a^2 + s}} = \frac{1}{2} \frac{1}{a^2 - b^2} \left( \frac{2a}{b^2} - S \right), \quad (18)$$

$$S = \int_0^\infty \frac{ds}{(b^2 + s)\sqrt{a^2 + s}} = \frac{2}{\sqrt{b^2 - a^2}} \arctan \frac{\sqrt{b^2 - a^2}}{a}, \quad (19)$$

where  $s$  is only an integration variable; the principal friction coefficients of translation (in the directions of the main axes)

$f_a$ ,  $f_b$ ,  $f_c$ , and of rotation (around the main axes)  $R_a$ ,  $R_b$ ,  $R_c$ , may be expressed as

$$\left. \begin{aligned} f_a &= \frac{16 \pi \eta}{S + a^2 A} & f_b = f_c &= \frac{16 \pi \eta}{S + b^2 B} \\ R_a &= \frac{16 \pi \eta}{3} \frac{1}{B} & R_b = R_c &= \frac{16 \pi \eta}{3} \frac{b^2 + a^2}{b^2 B + a^2 A} \end{aligned} \right\} \quad (20)$$

*Edwardes'* final formula of the friction coefficient of the rotating ellipsoid is wrong, since the numerical factor  $32/5$  must be replaced by  $16/3$  when the coefficient of the last term of the preceding equation is corrected to 4.

*K. Przibram*, 1912/14 (339, 340, 341), investigated experimentally the Brownian movement of ellipsoid particles, while *R. Gans* 1928 (145, 146, 147), and *F. Perrin* 1934/36, (328, 329), treated the problem theoretically.

In section III, § 35 (p. 110) of the present paper, the reader will find a brief deduction of the formula which describes the translational motion of an ellipsoid of revolution.

### § 23. THE ELECTRIC CHARGE OF THE COLLOIDAL PARTICLE.

Without giving historical data which may be found in the survey by *H. A. Abramson*, (5, pp. 17 and 40), it may be established that the conception of an electric double layer on the surface of the colloidal particles — similar to other interfaces — is not at all new.

In numerous experiments, the electric double layer has been proved to be a physical reality of greatest significance for the analysis of the reaction mechanism of colloids. Therefore, the most important theories of the structure of the double layer will be outlined here.

*Helmholtz-Smoluchowski's* theory from 1879 (185) and 1912/21 (385) considered the electric double layer to be a simple plano-parallel condenser, *i. e.* two infinitely thin surface charges at a constant distance.

On the boundary layer, however, osmotic and electrostatic forces develop which, according to the diffusion laws, tend to produce a continuous transition between these two phases. With



his hypothesis of the diffuse double layer, *G. Gouy*, 1909/17 (154—156), supposed the ion distribution to be in equilibrium with the mentioned forces.

*D. L. Chapmann's*, 1913 (64), and *K. F. Herzfeld's* application, 1920 (191), of *S. D. Poisson's* differential equation for the calculation of the ion distribution in the diffuse double layer prepared the way for *P. Debye* and *E. Hückel's* elegant ion theory, 1923 (77, 78), *E. Hückel*, 1924 (208), (*W. Orthmann*, 1927 (313), *H. Falkenhagen*, 1932 (111), and 1935 (112)).

Furthermore, *A. Gyemant*, 1923 (166), published a mathematical evaluation of *Gouy's* theory. *H. Müller*, 1933 (289), applied *Debye's* theory to the calculation of the ion distribution in the double layer. Finally, *O. Stern's* picture of the electric double layer, 1924 (396), represents a combination of the rigid *Helmholtz-Smoluchowski* layer and the diffuse *Gouy-Chapmann-Herzfeld* layer. A discussion of *O. Stern's* theory may be found in *F. Urban* and *H. L. White's* paper, 1932 (426).

The most recent studies of the double layer of colloidal particles may be found in the discussions of *The Faraday Society*, 1940 (113).

The charge of a colloidal particle may originate

- 1) from adsorption of ions from the dispersion medium,
- 2) from dissociation of molecules on the surface of the particles.

In the derivation of his brilliant ionization theory of the polyvalent ampholytes of a simple type, *K. Linderström-Lang*, 1924 (257), arrived at the same result assuming either adsorption or ionization.

- 3) The charge of particles may also develop as a so-called "phase boundary potential" (*W. Nernst*, cf. *L. Michaelis*, 1922 (276)) due to different ion activities in the two phases, medium and particle surface. However, this possibility does not exist if one phase is solid.
- 4) Finally, the charge of the particle may be the result of a combination of the mentioned possibilities.

*F. G. Donnan's* membrane potential (cf. *T. R. Bolam*, 1932 (40)), which is produced by an unequal distribution of the electrolyte in the two phases separated by the membrane, for

example plasma and erythrocyte content, can scarcely be considered the cause of the particle charge (*cf.* below).

In the older literature, *H. Netter*, 1925 (294), discussed the origin of the charge of the erythrocytes.

It is generally assumed that only the diffuse region of the double layer which may be moved relative to the boundary layer is decisive for the electrokinetic phenomena. *M. v. Smoluchowski*, 1912/21 (385), *A. Gyemant*, 1923 (166), *H. Freundlich*, 1930 (125, I, p. 356), and many others assumed that the electrokinetic potential can only be part of the total potential difference between the two phases (*Nernst's* thermodynamic potential). *Freundlich* denoted the electrokinetic potential also as  $\zeta$ -potential.

In the case of erythrocytes, the thermodynamic potential possibly corresponds to *Donnan's* membrane potential which is caused by an unequal electrolyte distribution between the plasma and the interior of the corpuscles. As regards the *Donnan* potential of red cells, it may be referred to the investigations by *E. J. Warburg*, 1922 (432), *O. M. Henriques*, 1929 (188) and 1935 (189), *E. Schiødt*, 1931 (368), and *T. R. Bolam*, 1932 (40). The magnitude of the *Donnan* potential is about 10 millivolts while the electrokinetic potential amounts to about 20 millivolts, both measured at the normal  $p_H$  of the blood. In contrast to *Smoluchowski's* and others' interpretations, the thermodynamic potential of the erythrocytes is less than their electrokinetic potential.

The question of the significance of the *Donnan* potential for the aggregation, however, is of extreme importance for the present paper and especially for the author's new aggregation theory (*cf.* § 38, p. 147). Since erythrocyte ghosts and intact erythrocytes — as discussed on p. 40 — show the same cataphoretic velocity, the electrokinetic potential of the red cells must be independent of the *Donnan* potential.

On account of the symbasy between the aggregation tendency of the erythrocytes and their electrokinetic potential which is independent of the *Donnan* potential it seems probable that the aggregation forces also lack connection with the *Donnan* potential. To support this view, we may point at the corresponding behaviour of erythrocyte- and erythrocyte ghost-aggregations in media with different electrolyte content. *F. Haffner*, 1922 (171), thus

found the best precipitation of erythrocyte ghosts in dialysates with the lowest content of electrolytes.

Presumably, it is generally true that the thermodynamic and the electrokinetic potentials are incommensurable magnitudes (cf. also R. Höber, 1926 (204, p. 755)).

H. B. Bull and R. A. Gortner, 1932 (51), used the electrokinetic measurements primarily as a means of obtaining the electric momentum (charge times thickness) of the double layer, and only secondarily for the determination of the  $\zeta$ -potential.

$\zeta$  is reduced by a reduction of the thickness of the double layer; this may explain the greatly discharging effect of the polyvalent ions. (Cf. H. Müller, 1928 (287), § 25 "Real coagulation theory etc.", p. 64).

Considering electrokinetic phenomena, *Helmholtz'* and *Gouy's* double layers (of the same thickness) are not equivalent. The reconstruction of a theory in agreement with *Gouy's* picture of the double layer has occupied numerous authors (cf. J. J. Bickermann, 1933 (36), where further references may be found).

If the radius of curvature of the particle surface is great compared with the thickness of the double layer, the constant of *Helmholtz'* equation becomes  $\frac{1}{4}\pi$  (H. A. Abramson, 1934 (5, p. 107)).

P. Debye and E. Hückel, 1924 (79, 80), found a value of  $\frac{1}{6}\pi$  in the case of ions the radius of which was small compared with the thickness of the ion atmosphere. This was also emphasized by M. Mooney, 1931 (282). D. C. Henry, 1931 (190), pointed out that the cataphoretic mobility of cylindrical particles must be dependent on their orientation if the *Debye-Hückel* theory is valid (cf. p. 39).

Since the electric conductivity of the suspensions does not directly enter *Helmholtz'* equation, the internal friction  $\eta$  of the medium becomes the most markedly temperature dependent factor. In the case of a silver hydrosol of low conductivity, E. F. Burton, 1906 (52), found the cataphoretic velocity  $v$  and the internal friction  $\eta$  to be inversely proportional, viz.

$$v\eta = \frac{1}{4\pi} \zeta D = \text{constant.} \quad (21)$$

Since the dielectric constant  $D$  is reduced with increasing tem-

perature, the electrokinetic potential  $\zeta$  must be correspondingly increased.

The cataphoretic velocity of colloidal particles depends on the electrolyte content and the  $p_H$  of the suspension fluid; in the case of red cells, *cf.* p. 39 (*Kozawa's* experiments) and p. 27.

As a consequence of the movement of a colloidal particle, an electromotive counter force appears due to displacements of the electric double layer (*H. Freundlich* (125, I, p. 10)) so that electric work must be performed (*cf.* *W. B. Hardy*, 1900 (176), and his interpretation of the electric double layer as a stabilizer described here on p. 64), which apparently increases the viscosity; this phenomenon is the so-called electro-viscous effect. On the basis of *Einstein's* viscosity formula, 1906 (96) and 1911 (98), *M. v. Smoluchowski* calculated a quantitative expression. Disregarding the high electric charge of the red cells, the electro-viscous effect is without any importance to the blood (NB. the high conductivity of the medium, the plasma).

*H. A. Abramson* and *L. S. Moyer*, 1936 (7), calculated the charge density on the erythrocytes of various animal species by means of a generalized *Gouy's* theory and starting from cataphoresis data available. In the case of large particles (*H. A. Abramson*, (5 p. 110), *H. A. Abramson* and *H. Müller* (8 and 9), and *J. A. Butler*, 1940 (56)), we get thus

$$\sigma = \sqrt{\frac{NDk\theta}{2000\pi}} \cdot \sqrt{\sum c_i \left( e^{-z_i \frac{e\zeta}{k\theta}} - 1 \right) + \sum c_j \left( e^{+z_j \frac{e\zeta}{k\theta}} - 1 \right)}, \quad (22)$$

where  $\sigma$  is the charge density,  $D$  the dielectric constant of the double layer,  $N$  *Avogadro's* number,  $k$  the *Boltzmann* constant,  $\theta$  the absolute temperature,  $e$  the electronic charge ( $4.77 \cdot 10^{-10}$  electrostatic units),  $\zeta$  the electrokinetic potential,  $z$  the ion valency, and  $C$  the concentration of ions ("in the body of the solution") in mols per litre. (A similar formula may be found in a paper by *R. Audubert*, 1933 (18)).  $\sigma$  has the same sign as  $\zeta$ ; all magnitudes are expressed in cm. g. sec., and electrostatic units (the c. g. s.-system). The density of charge times area gives the net charge of the particles, and dividing the net charge by the electronic charge leads to the number of electron charges per particle (*i. e.* the valency). If the electronic charge is assumed to fill

a space of  $10^{-15}$  cm<sup>2</sup>, that part of the particle which is covered with charge may be calculated; this surface hardly ever exceeds 1 per cent.

Human erythrocytes in an isotonic phosphate buffer at  $p_H = 7.4$  show a cataphoretic velocity of  $1.31 \mu/\text{sec}/\text{volt}/\text{cm.}$ , corresponding to an electrokinetic potential  $\zeta = 0.0168$  volt and a charge density of  $\sigma = 45\,000$  e. s. units. At an area of  $1.63 \cdot 10^{-6}$  cm<sup>2</sup>, the net charge becomes  $7.34 \cdot 10^{-3}$  e. s. units, in other words  $15.4 \cdot 10^6$  electronic charges which fill up 0.94 per cent of the erythrocyte surface.

Human erythrocytes carry the highest number of charges among all animal species investigated (*cf. Abramson and Moyer's table!*). Since *H. A. Abramson* investigating various types of anaemia found identical cataphoretic velocity of macro- and microcytes, the charge density must be regarded as the same. (Due to their greater area the greater cells show of course a greater net charge). *H. A. Abramson* and *L. S. Moyer* (*loc. cit.*) therefore assumed a mechanism which regulates the charge density, an idea which was set forth for the first time by *G. Hevesy*, 1917 (196), with respect to ions and colloidal particles. *Hevesy* supposed the existence of a relation between the size of the ions and the independence of ionic mobility of the charge; in the case of ordinary ions, he assumed the ratio ion charge : radius to be constant. The charge of colloidal particles increases with the square of the radius.

In connection with the electric charge of colloidal particles as a decisive factor for the aggregation process, the structure of the solution may claim some interest.

In order to explain the behaviour of different colloids, a theory reappeared from time to time, *viz.* that water might be adsorbed to the surface of the colloidal particle — similar to the hydration theory of ordinary electrolytic ions. (*Cf. R. Fåhræus' hypothesis as regards the corpuscle surface, p. 43.*)

The concept of "adsorbed water", however, led to the delusive idea of water which should be more or less bound to the surface of the particle. On the basis of recent X-ray investigations (for literature, *cf. S. S. Kistler*, 1932 (226), and *G. W. Stewart*, 1939 (399)), it must, however, be assumed that the molecules of the solvent are continuously associated to unstable complex com-

pounds of crystal-like structure (*Stewart's* cybotactical complexes, *Kistler's* cybomas).

The existence of these molecule associations in the solvent were used by *S. S. Kistler* (*loc. cit.*) in order to explain the aggregation of hydrophobic particles. In spite of the fact that this question belongs to the treatment of the real coagulation theory (*cf.* § 25, p. 64) the theory may be outlined in brief. If the surface of a particle is indifferent, it will reflect all cybomas which might hit it. A hydrophilic and a hydrophobic surface will give rise to increased formation or disintegration, respectively, of cybomas, so that more or less cybomas will be found at a hydrophilic or hydrophobic surface. If the hydrophobic particles approach each other, they are forced closer together due to the surrounding cybomas which show a high diffusibility as a cause of their smallness (*however, cf. the critical remarks concerning N. Rashevsky's hypothesis, here p. 193*); inversely, hydrophilic particles will repulse each other. The author has refrained from any attempt to apply this hypothesis to erythrocyte aggregations.

## § 24. METHODS OF MEASURING COAGULATION\*).

### A. Direct methods.

1) Since the forces interacting between the particles of a colloidal solution determine their aggregation and thus the coagulation of the colloid, the ideal investigation of this process should aim at the determination of these forces. However, no such method is known, and the quantitative course of coagulation has therefore been studied by measuring the "rate of coagulation" (*H. Freundlich, 1932 (125, II, p. 114)*).

2) In the counting method, the microscopic or ultramicroscopic estimation of the number of particles at various times is applied.

### B. Indirect methods.

In connection with the counting method, the application of the sedimentation analysis to coagulating systems should be

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\*) In this paper, the term "coagulation" is used in the colloid chemical sense, only — flocculation or aggregation — without taking the reversibility or irreversibility of this process into consideration.

mentioned, since it has in view to determine quantitatively the dispersion degree of the system to be investigated by means of measuring the quantity of the different aggregates (granulometry). As, however, in sedimentation analysis several indirect methods are applied, it has been included in a number of indirect methods.

- 1) Optical methods of observation either of the transparency of the colloidal sol or of the intensity of its *Tyndall* phenomenon ("Tyndall cone").\*)
- 2) Measurement of the viscosity of the sol.
- 3) Determination of the electric conductivity of the sol.
- 4) Measurement of the flocculation by means of specific gravity estimations of the suspension; direct weighing of the sediment, or
- 5) Quantitative chemical analysis of the flocculated mass, etc.

## § 25. REAL COAGULATION THEORY, CRITICAL POTENTIAL THEORY, ETC.

Ions are the most sensitive regulators of the colloidal state, especially in the case of hydrophobic colloids which show low stability.

*W. B. Hardy*, 1899 (175) and 1900 (176, 177), was the first to observe a certain relationship between the electrolyte sensitivity of the colloids and the change of sign of their cataphoretic migration velocity. He noticed that thermodenaturated egg albumin sol was stable in acid and alkaline solutions where it moved to the cathode and anode, respectively, while precipitation occurred just at the »isoelectric point« (*Hardy*) where the migration velocity was zero.

*Hardy* (176) considered the electric double layer to be the cause of colloid stability, since the double layer would resist to a particle movement, thus counteracting the performance of electric work. (However, the electro-viscous effect due to its minute order of magnitude does not play any part in this connection; cf. p. 61).

The ability of salts to produce precipitation of colloids was already known to *Th. Graham*. *Hardy* observed that the charge

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\*) The principle used is generally denoted as nephelometry.

of the coagulating ion was always opposite to that of the colloidal particle (*Hardy's* law of precipitation), and the investigations carried out by *H. Schulze*, 1882/83 (374, 375), concerning the coagulation power of various salts on arsenic trisulfide sol revealed that the coagulation ability increased with increasing ion valency (*Schulze's* valency rule, cf. *W. Ostwald*, 1920 (319)).

Coagulation in relation to cataphoresis of the particles was studied quantitatively by *E. F. Burton*, 1906 (52, 53), 1909 (54) and 1926 (55), *R. Ellis*, 1912 (103, 104), *F. Powis*, 1914 (337) and 1916 (338), and *H. Freundlich* and *H. P. Zeh*, 1925 (129).

The creators of the so-called critical potential theory, *R. Ellis* and *F. Powis*, studied oil emulsions (without emulsifier) and they improved *Hardy's* isoelectric theory. While this theory only permitted coagulation at the particle potential zero and therefore not actually explained the stability of colloidal solutions, *Ellis* and *Powis* were able to prove that emulsions and suspensions are stable only as long as the electrokinetic potential of the particles exceeds a given critical value. As soon as the critical potential is reached, the colloid becomes instable and begins coagulating, the rate of coagulation increasing with decreasing potential.

In the case of oil emulsions, *F. Powis* (*loc. cit.*) found almost the same value of the critical potential (c. 30 millivolts) for all electrolytes. His later investigations of arsenic trisulfide sol, however, revealed that this potential is not the same for different cations (cations, since  $\text{As}_2\text{S}_3$  is a negative colloid). Different ions of the same valency can frequently be ordered in *Hofmeister's* lyotropic series according to their coagulation power. The ions seem to produce changes in potential which are in some relation to their position within the ionic series. This interesting phenomenon has first been observed by *A. Westgren* (440) on gold suspensions and has been investigated thoroughly by *P. Tuorila* on gold suspensions, 1926 (421), and on paraffin-, clay-, quartz-, and sodium permutoxide suspensions, 1928 (423).

In principle, the decrease in electrokinetic potential of hydrophobic particles cannot exclusively be caused by a reduction of the charge of the particle, but it must moreover originate partially in a reduction of the thickness of the electric double layer. In



this connection, *H. Müller's* quantitative hypothesis, 1928 (287), is very remarkable, inasmuch as it explains the reduction of the electrokinetic potential after addition of oppositely charged ions of different valencies by a change of the thickness of the diffuse double layer.

Also *H. Freundlich*, *K. Joachimsohn* and *G. Ettisch*, 1929 (128), supposed that coagulation appears when the  $\zeta$ -potential is reduced to a given critical value, however, this is not identical with a discharge of the particles.\*) In numerous cases, in re-charge phenomena for example, where the variation of the electrokinetic potential with the electrolyte concentration cannot exclusively be explained by a change of thickness of the double layer, it must furthermore be assumed that the charge of the particles changes due to ion adsorption.

Since the total surface of the particles towards the dispersion medium is reduced by aggregation, numerous authors (*F. G. Donnan*, 1903 (84), *A. Gyemant*, 1926 (167), *A. March*, 1927 (271), *W. C. M. Lewis*, 1932 (253), and others) considered this part of the coagulation process a direct consequence of interfacial tension; the stable state of the suspension should be attained by reduction of the surface energy of the particles due to the electrostatic forces of the electric double layer.

It seems difficult to find an agreement between *Gyemant's* and *Lewis's* theories which admit the existence side by side of particles of different sizes and the *Wiegner-Galecki* effect described on page 75.

On the basis of thermodynamic calculations, *A. March* (*loc. cit.*) found the measured electrokinetic potentials to be about 10 times too small to secure stability during electric repulsion. Therefore he assumed — as already adopted previously by *W. Ramsden*, 1904 (346), *F. G. Donnan* and *H. E. Potts*, 1910 (85) — that the particles are shielded by a highly viscous skin. *H. Müller*, 1935 (291), explained the existence of this skin by means of the electrostriction of the medium due to the electric field in the double layer.

*S. S. Kistler's* theory of coagulation of hydrophobic particles has been described in a preceding section (p. 63).

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\*) *Addendum*: Cf. *H. A. Abramson's* remarks (113, p. 14) concerning the influence of salts on the cataphoretic velocity of the particles.

## § 26. GENERAL COAGULATION THEORY. INTRODUCTION.

*G. Wiegner*, 1928 (446), published an excellent survey of the general coagulation theory of hydrophobic colloids which will be discussed in the following.

According to the critical potential theory, coagulation occurs as soon as the charge of the particles has fallen below a given (critical) value. In agreement with the statistical-mechanical interpretation, not all particle collisions take place with the same energy and, consequently, only part of the collisions will cause aggregation. With decreasing potential, the effective collisions are more frequent and they reach a maximum at the potential zero.

According to *R. Zsigmondy* and *M. v. Smoluchowski* (387), we must differentiate between "slow" and "rapid" coagulation. If only a fraction of all collisions results in aggregation, the system is in a state of "slow" coagulation; if, however, aggregation takes place at every collision, we speak of "rapid" coagulation. "Rapid" coagulation means only that state in which aggregation occurs with a given maximum speed, without taking into account whether the time necessary for coagulation is long or short. If the collision of particles due to their Brownian movement is equally probable in all directions, the phenomenon is termed "perikinetic coagulation" (*G. Wiegner*). If the probability of collision is greater in one direction than in other directions — for example, in the case of large particles moving relative to small ones due to gravity or centrifugal force — the state is termed "orthokinetic coagulation" (*G. Wiegner*).

If the colloidal system exclusively contains particles of uniform size, we may speak of a monodispersive system. Systems with particles of two or several different sizes may be denoted as bidispersive and polydispersive, respectively. Slow or rapid perikinetic coagulation may take place in monodispersive or polydispersive systems, while the appearance of (slow or rapid) orthokinetic coagulation seems to be restricted to polydispersive systems.

## § 27. SMOLUCHOWSKI'S MATHEMATICAL COAGULATION THEORY ("SLOW" AND "RAPID" PERIKINETIC COAGULATION OF MONODISPERSIVE SYSTEMS).

On the basis of *Zsigmondy's* findings, *Smoluchowski* (387) developed the first useful coagulation theory. Even though his

theoretico-physical investigations — owing to their nature — are based upon a number of “ideal” suppositions which hardly are fulfilled to completeness, his theory describes almost quantitatively the coagulation of hydrophobic colloids.

The suppositions of the theory may be summarized as follows

- 1) that particles and micelles are spherical,
- 2) that the original colloid is monodispersive and that an approximate monodispersity is prevailing during coagulation;
- 3) that each particle is surrounded by a given sphere of action where the attractive (adhesive) forces are so great that the particles unite “permanently”; the forces outside the sphere are put equal to zero,
- 4) that the frequency of collision of particles is determined by the Brownian movement,
- 5) that other movements of the micelles due to sedimentation, stirring, etc., can be disregarded,
- 6) that only the stationary (*i. e.* time independent) distribution of particles round the nuclei of condensation is of any significance for coagulation,
- 7) that the tendency to aggregation is the same for micelles of any (arbitrary) multiplicity.

The third supposition — that the forces interacting between the particles can be described by such a sphere of action — signifies an essential simplification of the mathematical evaluation. The author's calculations concerning the dependence of the radius of action on the intercorpuseular forces prove that this assumption may lead to reasonable results (*cf.* p. 97).

*Smoluchowski* calculated the average number of particles which due to their Brownian movement within a given space of time enter the sphere of action surrounding an arbitrary particle which must be considered temporarily immobile and forming a nucleus of condensation.

Since a diffusion process may be regarded as the macroscopic manifestation of the Brownian movement, the present problem can be solved by calculating a corresponding diffusion problem. If the nucleus of condensation is assumed to be a completely absorbent sphere floating in the centre of an infinite medium,

the solution of the diffusion equation (written according to the formula of spherical symmetry) must satisfy the following boundary conditions.

At any time, the concentration of particles on the surface of the sphere of action must be zero, while outside this surface it must have a constant value at the time zero.

*Smoluchowski's* expression for the indiffused amount of particles consists of two components, one of which is time independent and one dependent on time, the influence of which, however, subsides very rapidly after beginning coagulation.

On account of the time dependent component, the quantity coagulated per unit of time will be somewhat greater in the beginning, since the concentration of particles exactly around the nuclei of condensation decreases below the constant value found everywhere at the time zero. As soon as such a decrease in concentration is established round the nuclei of coagulation, the state will become stationary, since just as many particles will diffuse in as will be captured by the nucleus of condensation.

In his preliminary calculations, *Smoluchowski* assumed the nucleus of condensation to be immobile; however, as this nucleus is a random particle performing Brownian movements just as all other particles, this property has to be taken into account. Since coagulation is determined exclusively by the relative movements of the nucleus and the particle, *i. e.* a new Brownian movement with a corresponding diffusion constant equal to the sum of the respective diffusion constants, *Smoluchowski* reckons with a mutual diffusion constant twice that of the individual particles.

Finally, the concentration of the various aggregates at any time may be determined by solving a system of simultaneous differential equations similar to those known from the kinetics of some chemical processes or from the disintegration of radioactive substances, where a number of intermediate products are formed and later transformed again.

If  $\nu_0$  denotes the initial number of particles per unit volume at the time  $t = 0$ , and  $\nu_1, \nu_2, \nu_3$  *etc.* the numbers of single, double, triple *etc.* particles, the total number of particles is

$$\sum \nu = \nu_1 + \nu_2 + \nu_3 + \dots \quad (23)$$

determined by the differential equation

$$\frac{d\sum v}{(\sum v)^2} = -a dt, \quad (24)$$

where  $a = 4 \pi D R$ , as  $D$  is the diffusion constant, and  $R$  the radius of the sphere of action. If the number of particles is expressed as a fraction of the total number,  $a dt$  gives the number of particles caught up by an arbitrary nucleus of condensation in the time interval  $dt$ . The magnitude  $a$  has often been termed coagulation probability.

With the initial condition  $\sum v = v_0$  at  $t = 0$ , we get

$$\sum v = \frac{v_0}{1 + av_0 t} = \frac{v_0}{1 + 4\pi DR v_0 t} = \frac{v_0}{1 + \frac{t}{T}}. \quad (25)$$

The constant  $T = \frac{1}{av_0}$ , which has the dimension of a time, is called (half) the coagulation time. If  $t = T$  we get  $\sum v = \frac{v_0}{2}$ .

On the basis of the result for  $\sum v$ , *Smoluchowski* was able to integrate the other differential equations and he obtained thus the following expression for the different particles

$$\left. \begin{aligned} v_1 &= v_0 \frac{1}{[1 + av_0 t]^2} & v_2 &= v_0 \frac{av_0 t}{[1 + av_0 t]^3} \\ v_3 &= v_0 \frac{[av_0 t]^2}{[1 + av_0 t]^4} & v_k &= v_0 \frac{[av_0 t]^{k-1}}{[1 + av_0 t]^{k+1}} \end{aligned} \right\} \quad (26)$$

The number of  $k$ -fold particles reaches a maximum at

$$t = \frac{k-1}{2} T, \quad (27)$$

and this maximum amounts to

$$v_k = 4v_0 \frac{(k-1)^{k-1}}{(k+1)^{k+1}}. \quad (28)$$

$v_1$  and  $\sum v$  decrease rapidly in the beginning and slowly later on,  $v_1$  decreasing more rapidly than  $\sum v$ ;  $v_2, v_3$ , etc. increase from zero, passing a maximum at a more and more delayed time, finally decreasing again.

The comparison of coagulation measurements is based upon so-called "reduced" curves, where the relative number of particles  $\frac{\Sigma v}{v_0}, \frac{v_1}{v_0}, \frac{v_2}{v_0}, \frac{v_3}{v_0}, \text{ etc.}$  is plotted against  $\frac{t}{T}$ , the time in multiples of the coagulation time. In this way (Fig. 1, below) a satisfactory picture of the course of coagulation is attained.

Decrease in the number of different particles during "rapid" monodispersive coagulation (according to *M. v. Smoluchowski*, 1917 (387)).

Ordinates:  $\frac{v}{v_0}$ , number of particles as fractions of the initial number of single particles,  $v_0$ .

Abscissae:  $\frac{t}{T}$ , time  $t$  in multiples of the coagulation time  $T$  (denoted as  $\frac{t}{\S}$  on the figure).

$\Sigma v$  is the total number of particles,  $v_1, v_2, \text{ etc.}$  the number of single, double, etc. particles.

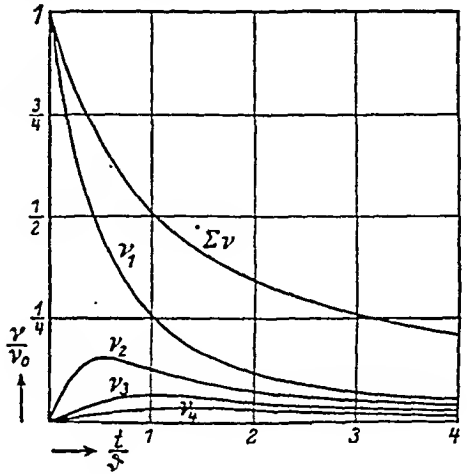


Fig. 1.

How far coagulation follows *Smoluchowski's* theory may be decided by investigating

- 1) whether the attraction radius is constant in the course of an experiment;
- 2) whether the attraction radius is constant at different initial concentrations or, in other words, whether the initial concentration is inversely proportional to the time of coagulation ( $v_0 T = \text{constant}$ );
- 3) whether the coagulation probability  $\alpha$  is independent of the radius of the particle, since

$$\alpha = \frac{1}{v_0 T} = 4 \pi D R = \frac{2}{3} \frac{k \Theta}{\eta} \frac{R}{r}, \quad (29)$$

where  $R$  increases proportional to  $r$ ;  $k$  is the *Boltzmann* entropy constant,  $\Theta$  the absolute temperature, and  $\eta$  the viscosity coefficient of the suspension medium;

- 4) whether  $\alpha$  at various temperatures is proportional to  $\frac{\Theta}{\eta}$ .

The importance of the radius of attraction is most readily under-

stood by studying the ratio between attraction radius and particle radius,  $\frac{R}{r}$ .

If  $\frac{R}{r} = 2$  (hence  $R = 2r$ ), coagulation occurs only by touching.

If  $\frac{R}{r} > 2$ , aggregation takes place only, according to *Smoluchowski*, when the distance between the centres of gravity of the particles is smaller than or equal to  $R$ .

If  $\frac{R}{r} < 2$ , *Smoluchowski* assumes that only a fraction  $\epsilon$  of the collisions between the particles results in coagulation; on this basis, he develops his theory of "slow" coagulation, where  $\alpha$  is replaced by  $\alpha\epsilon$ .

*Smoluchowski's* theory of rapid coagulation was confirmed by a number of investigations.

*R. Zsigmondy*, 1917 (460), determined ultramicroscopically the decrease in the total number of particles  $\Sigma \nu$  in a gold sol which was brought to rapid coagulation by addition of electrolytes. The number of individual particles was calculated on the basis of the mean value of  $\frac{1}{T}$  which was constant during the single experiment, except for the very first moment. As the single particles in these experiments appeared green, the aggregates, however, yellow, *Zsigmondy* was able to determine the number of single particles, and his values were in good agreement with the calculated numbers at different times. The values of  $\frac{R}{r}$  obtained varied between 2 and 3.

When investigating the variation of  $\Sigma \nu$  in a gold sol, *A. Westgren* and *J. Reitstötter*, 1917 (442), found  $\frac{R}{r} = 2.3$  (mean value). The course of coagulation was independent of the size of the particles within rather wide limits.

*A. Ehringhaus* and *R. Wintgen*, 1923 (92), who studied the coagulation of gold particles in the borax pearl at  $925^{\circ}\text{C}$  and determined the decrease of  $\Sigma \nu$  with the time of glowing, found  $\frac{R}{r} = 2.3$ , except for one experiment where  $\frac{R}{r} = 13.7$ .

*H. R. Kruyt* and *A. E. van Arkel*, 1920 (234), investigated selenium sols.

*H. Lachs* and *S. Goldberg*, 1922 (240), as well as *M. Garner* and *W. C. M. Lewis*, 1926 (148), made experiments with gold sols at different temperatures and they proved, in agreement with *Smoluchowski's* theory, an approximate proportionality between  $\alpha = \frac{1}{\nu_0 T}$  and  $\frac{\Theta}{\eta}$ .

When measuring gold-, paraffin-, clay-, and graphite suspensions, *P. Tuorila*, 1927 (422), recorded values of  $\frac{R}{r}$  between 2 and 3. The size of the particles was without any influence on the course of coagulation.

*Smoluchowski's* formulas of slow coagulation have also repeatedly been checked experimentally.

*A. Westgren*, 1918 (440), performed comprehensive measurements on gold sols, and *H. Lüers*, 1920 (268), investigated the flocculation of Congo Rubin sols. The results of both authors confirm the theory.

As an essential disagreement with the theory we must consider *S. Odén's* experiments on sulfur and silver sols, 1920 (303), *P. Tuorila's* measurements on gold sols (421), and the studies of a few others, revealing that the rate of slow coagulation depends on the size of the particles. Within the same system, large particles coagulate more rapidly than small ones and, hence, the fraction ( $\epsilon$ ) of effective collisions must be greater in the case of large than of small particles. According to the theoretical considerations by *H. Müller* (287, p. 307),  $\epsilon$  increases with increasing radius of the particles.

## § 28. PERIKINETIC COAGULATION OF POLYDISPERSIVE SYSTEMS.

When calculating the coagulation of a monodispersive system, *M. v. Smoluchowski* (387) assumed that multiple particles formed during coagulation have radii of action which are proportional to the radii of the approximately spherical aggregates.

The radius of action  $R_{ik}$  at the collision between two aggregates of the radii of action  $R_i$  and  $R_k$ , in analogy to the molecular gas theory, is equal to

$$R_{ik} = \frac{1}{2} (R_i + R_k). \quad (30)$$



Since, according to *Einstein* (cf. p. 56), the diffusion coefficient of a sphere is inversely proportional to the radius, we get

$$D_{ik}R_{ik} = \frac{DR}{2} \frac{(R_i + R_k)^2}{R_i R_k}, \quad (31)$$

where  $D$  and  $R$  are diffusion coefficient and radius of action, respectively, of the single particles.

If  $R_i = R_k$ , we get

$$D_{ik}R_{ik} = 2DR$$

and

$$2\pi D_{ik}R_{ik} = 4\pi DR = \alpha, \quad (32)$$

which means that the coagulation probability of the aggregation of two multiple particles whose radii do not differ essentially is equal to the coagulation probability of two single particles.

If the coagulation probability of the particles  $i$  and  $k$  is denoted as  $W_{ik}$ , we get

$$W_{ik} = 2\pi R_{ik}D_{ik} \quad (33)$$

and, in the case of equal particles,

$$W_{ii} = 2\pi R_{ii}D_{ii}. \quad (34)$$

Since the diffusion coefficient is

$$D_i = \frac{k\Theta}{6\pi\eta r_i}, \quad (35)$$

we obtain

$$W_{ii} = \frac{2}{3} \frac{k\Theta}{\eta} \left( \frac{R_{ii}}{r_i} \right) = \alpha, \quad (36)$$

where  $R_{ii}$  is assumed to be proportional to  $r_i$ , hence  $\frac{R_{ii}}{r_i} = \frac{R}{r}$ .

On account of the independency of the coagulation probability of the radius of the particles, the coagulation time of the monodispersive system depends on concentration and is independent of the dispersion degree.

During coagulation of a monodispersive colloid, the system becomes more and more polydispersive, since multiple particles are formed and, therefore, aggregates of a rather small difference in radius exist only for some time after beginning coagulation. *Smoluchowski's* formulas can therefore only be expected to be valid in this initial state.

*H. Müller's* coagulation theory (286—288) of polydisperse systems takes into account especially one fact which was substantiated theoretically by *Smoluchowski* (387) and proved experimentally by *G. Wiegner* (445) and *A. Galecki* (143), viz. that the coagulation probability is greater for particles of unequal size than for equal ones, i. e. that large micelles behave like nuclei of coagulation.

*H. Müller* succeeded in giving the following mathematical formulation of the simplest possible polydisperse system, viz. the bidisperse system.

In the beginning, we find  $N_0$  large particles and  $n_0$  small ones per cc. The radius of the large particles  $\rho$  is assumed to be many times greater than the radius of the small particles,  $r$ .

According to *Smoluchowski*, the coagulation probability of two small particles or of aggregates of small particles is

$$W_r = 4 \pi R_r D_r, \quad (37)$$

where  $R_r$  is the radius of action.

In the case of large particles and complexes which contain at least one large particle, the probability of aggregation is

$$W_\rho = 4 \pi R_\rho D_\rho = W_r. \quad (38)$$

In the case of aggregations of small particles — or complexes containing only small particles — with large particles or complexes with at least one large particle, we get

$$W_{\rho r} = 2 \pi R_{\rho r} (D_r + D_\rho). \quad (39)$$

*Müller* assumed that the particles must touch in order that coagulation occurs, and he found

$$W_{\rho r} = \gamma_{\rho r} W_{rr} \quad (40)$$

with a probability factor  $\gamma_{\rho r}$ ,

$$\gamma_{\rho r} = \frac{(1 + V_\rho)^2}{4 V_\rho} \quad (41)$$

which is greater than 1, where  $V_\rho = \frac{\rho}{r}$  is the ratio of the radii of large and small particles (which are retained when dealing with complex particles).

In analogy to *Smoluchowski*, a system of an infinite number of

differential equations is assumed for the changes of the different numbers of particles.

By introduction of

$$\sum \nu = \sum_{i=1}^{k-1} \nu_i = \text{total number of small particles and}$$

$$\sum N = \sum_k \nu_k = \text{total number of large particles}$$

and by interpreting the originally large particles as complexes of  $k$  small ones and, finally, by integration we get

$$\sum \nu + \sum N = \frac{N_0}{1 + \frac{t}{T_{N_0}}} \left[ 1 + \frac{\lambda}{(V_n \lambda + 1) \left( 1 + \frac{t}{T_{N_0}} \right)^\lambda - 1} \right]. \quad (42)$$

In this equation,  $V_n = \frac{N_0}{n_0}$  is the ratio of the initial number of large and small particles, and  $T_{N_0}$  is the coagulation time of large particles, *i. e.*

$$\sum N = \frac{N_0}{1 + \frac{t}{T_{N_0}}}, \quad \sum N = \frac{N_0}{2} \text{ at } t = T_{N_0}. \quad (43)$$

$\lambda = 2\gamma - 1 = \frac{V_p^2 + 1}{2V_p}$  is Müller's factor, where  $V_p = \frac{\rho}{r}$  is the ratio of the radii of the large and small particles.

From Müller's formula, a mathematical discussion of which may be found in *P. Tuorila's* paper (421), we conclude,

1) The coagulation of bidispersive systems occurs more rapidly than the coagulation of a system with the same number of large particles but no small ones.

2) If many large particles are present and only a few small ones, the small particles will be captured by the large ones within a short time and the whole system will coagulate as if it consisted of large particles, only, *i. e.* monodispersively.

3) If many small particles are present and only a few large ones, then the system will also coagulate monodispersively.

4) The difference between monodispersive and polydispersive coagulation can first be demonstrated when the ratio  $V_p$  at least

exceeds 10. If the ratio is below 10, *Smoluchowski's* formula is a satisfactory description of the course of coagulation.

5) Considerable deviations from the monodispersive course are found when large particles are present in a moderate number already in the beginning of coagulation and, furthermore, when the time of observation, *i. e.* the lapse of time until the number of particles of the system is determined, is relatively small.

Even if the number of large particles is moderate, the number of small particles must be rather great, since otherwise the small particles will soon be captured by the large ones and the system will coagulate as if it consisted of large particles, only.

In the case of polydispersive systems we have, furthermore, the following rules.

Coagulation occurs the quicker, the greater the number of particles. After the lapse of a long time, the number of particles is independent of the number in the beginning of coagulation, in analogy to coagulation in a monodispersive system; the number of particles of polydispersive systems becomes equal to the number of particles of monodispersive systems.

*H. Müller's* theory was confirmed by *P. Tuorila's* excellent experiments (*G. Wiegner* and *P. Tuorila* (449), *P. Tuorila* (421 and 422) ).

In coagulation of polydispersive systems, *Smoluchowski's* ratio  $\frac{R}{r}$  (radius of action / radius of particle) does not exceed the value 7 — not even in the case of extreme polydispersity (*G. Wiegner* and *P. Tuorila, loc. cit.*).

## § 29. ORTHOKINETIC COAGULATION.

During coagulation of dispersive systems, where large particles either are present in advance or are produced rapidly by aggregation and begin sedimenting, the coagulation process may be affected in a characteristic way by an increase in the number of collisions in vertical direction. In contrast to the usual "perikinetic" coagulation which is exclusively caused by Brownian movements this process is termed "orthokinetic" coagulation, as suggested by *G. Wiegner* (*cf. P. Tuorila* (422) ).

*P. Tuorila* treated the orthokinetic coagulation experimentally and theoretically (quartz-, clay-, and gold suspensions). His theory is based upon the assumption of a hollow cylindrical coagulation space ("skin space" or "Hautraum") for large particles. The outer radius of the coagulation space is set equal to the radius of the sphere of attraction, and the inner radius equal to the radius of the particle. The height of the cylinder is proportional to the difference between the rate of fall of large and small particles, as determined by *Stokes'* formula and, furthermore, to the time during which the large particle is in action. A particle which penetrates the surface of the coagulation space ("skin of coagulation" or "Koagulationshaut") is coagulating. This simple work hypothesis which — by *Tuorila's* theory — led to useful results has been further improved by *H. Müller* (288) (cf. below, p. 82) who took into consideration the course of the lines of flow around the large particles.

The size of the attraction space determining the orthokinetic coagulation effect depends on the function

$$r_p \left( 2 + \frac{r_p}{R_p} - 2 \frac{r_p^2}{R_p^2} - \frac{r_p^3}{R_p^3} \right), \quad (44)$$

where  $r_p$  and  $R_p$  denote the radii of large and small particles, respectively (bidisperse system).

In the case of  $r_p = 0$  or very small, *i. e.* if the small particles are very small compared with the large ones, no orthokinetic coagulation occurs.

If  $\frac{r_p}{R_p} = 1$ , the coagulation space is equal to zero, in other words, monodisperse systems do not show orthokinetic coagulation.

Between  $\frac{r_p}{R_p} = 0$  and  $\frac{r_p}{R_p} = 1$  the mentioned function passes a maximum at 0.6, which means that the orthokinetic coagulation effect is greatest when the ratio between the radii is 0.6. The size of the coagulation space is furthermore proportional to the number of large particles. As regards the formulas of the average number of particles per cc at various levels, we must refer to the original papers.

In the case of slow orthokinetic coagulation, *Tuorila* stated similar considerations.

In a number of special cases, it seems unnecessary to pay regard to the orthokinetic coagulation, *viz.*

1) In systems with many small and many large particles, the number of small single particles is reduced very rapidly due to perikinetie, polydispersive coagulation.

2) At a very high number of large particles, the small ones coalesce rapidly with the large particles.

3) If the number of small particles is moderate or high and the number of large particles is low, the coagulation is monodispersive as if no large particles were present.

In certain systems with so-called "autocatalytic" coagulation (*H. Freundlich*, 1932 (125, vol. II, 160)), the rate of coagulation increases slowly in the beginning and then passes a maximum.

According to *P. Tuorila* (422), this variation of the coagulation velocity may be explained by means of orthokinetic coagulation. If we assume a system where the initial number of particles is small, perikinetie coagulation would be almost without any influence (*M. v. Smoluchowski* and *H. Müller*) compared with the orthokinetic coagulation. In the beginning, we assume  $N_0$  large particles and  $n_0$  small particles with the radii  $R_p$  and  $r_p$ , respectively; the size of the "skin space" of the large particles be denoted as  $B$ , hence the small particles decrease by  $dn$  in the time  $dt$ , so that

$$dn = - \text{constant } nB dt. \quad (45)$$

If the number of particles is given per cc and the "skin space" volume in cc, the proportionality constant becomes equal to 1, and thus

$$dn = - nB dt. \quad (46)$$

With the initial condition  $n = n_0$  at  $t = 0$  we get by integration

$$n = \frac{1}{c} e^{-\int_0^t B dt} = n_0 e^{-\int_0^t B dt}, \quad (47)$$

since the integral  $\int B dt$  vanishes at the time zero.

If we assume that the "skin space" is constant during coagulation — which is only permissible in a short time interval, since the large particles grow due to association with small ones —

the last mentioned formula may be written

$$n = n_0 e^{-B_0 t}. \quad (48)$$

If

$$V_m = \frac{n_0 r_p^3}{N_0 R_p^3} \quad (49)$$

is the ratio between the masses of the large and small particles,  $B$  varies according to the expression

$$B = \text{constant} [1 + V_m - V_m f(t)] \quad (50)$$

when  $\frac{r_p}{R_p} < 0.4$ .

We do not know the precise value of the numerical factor  $f(t)$  to which the number of small particles is proportional, but as a first approximation we may consider

$$f(t) = e^{-B_0 t}. \quad (51)$$

After introduction of this value into  $n = n_0 e^{-\int B dt}$  we get

$$n = n_0 e^{-\int B_1 dt}. \quad (52)$$

If

$$f(t) = e^{-\int B_1 dt} \quad (53)$$

is used as a new approximation, we obtain

$$n = n_0 e^{-\int B_m dt}. \quad (54)$$

If  $m$  is sufficiently great so that  $B_{m-1} = B_m$ , this last mentioned expression leads to the correct value of  $n$ .

The orthokinetic coagulation is much more pronounced above  $V_m = 8$  than for  $V_m$  somewhat above zero, and it is then of a markedly autocatalytic type. The number of particles decreases slowly in the beginning, since the few large particles can only capture a few small ones. However, the effect of the large particles increases rapidly due to their increased radius on account of association with small particles. Later, the coagulation effect decreases when the large particles are very large compared with the small ones.

Coagulation curves calculated according to *Tuorila's* method lead to S-shaped  $n - t$  curves (cf. *Tuorila* (422, Fig. 7, p. 109)). According to *H. Gessner*, 1931 (151), the S-curve of the sinking

reaction represents a system coagulating orthokinetically. (The author's objection to this view will be discussed on p. 168).

The hydrodynamic interchange between two spheres which move in a viscous medium has been investigated by *M. v. Smoluchowski*, 1911 (384), *C. W. Oseen*, 1912 (315) and 1927 (317), *H. Faxén*, 1925 (115) and 1927 (116), and *M. Stimson* and *G. B. Jeffery*, 1926 (400). Any influence upon the aggregation process, for example the possibility for an orthokinetic coagulation of a monodispersive system, can hardly be ascribed to this effect.

### § 30. STREAMING COAGULATION.

A change of the coagulation process caused by the movements of micelles relative to one another due to a superposed (stationary) streaming is called streaming coagulation. A special case of streaming coagulation has been discussed above, *viz.* the orthokinetic coagulation which is produced under the influence of sedimentation. Another example is the effect of stirring and centrifuging upon coagulation.

*Smoluchowski*, 1917 (387), made the first attempt to give a theoretical treatment of streaming coagulation and he pointed out that the different velocities of fluid layers during laminar flow, for example during slight stirring, must lead to collisions of the suspended particles, even if their Brownian movements are extremely small.

*Smoluchowski* calculated the ratio  $\beta$  between the number of particles which are introduced into the sphere of action of the coagulation nucleus by stirring, and the number of particles which would diffuse into this sphere due to their Brownian movements.

When considering a particle (radius  $r_p$ , radius of action  $R$ ) which rests in the origin of a rectangular coordinate system ( $X, Y, Z$ ) with a laminar streaming parallel to the  $X$ -axis along the  $Y, X$ -plane in such a way that we find a decrease in velocity  $\left(\text{gradient } \frac{du}{dz}\right)$  with the  $Z$ -axis whereby the particles reach relative velocities which are proportional to the distance of the respective liquid layer from the  $Y, X$ -plane, we get



$$\beta = \frac{1}{6\pi} \frac{du}{dz} \frac{R^2}{D} = \frac{4\eta r_p^3}{k\Theta} \frac{du}{dz}, \quad (55)$$

since  $R = 2 r_p$ .

In this equation,  $D$  is the diffusion constant of the particles,  $\eta$  the coefficient of internal friction of the suspension fluid,  $k$  the Boltzmann constant, and  $\Theta$  the absolute temperature.

If the velocity gradient  $\frac{du}{dz} = 1$ ,  $\beta = 10^{-5}$  for submicrons with a radius of  $24 \mu\mu$ , while we get for microns with a radius of  $1 \mu$   $\beta = 1$ .

Slight stirring is thus without any influence upon the coagulation of amicrons and submicrons, while the coagulation of microns and still larger particles is vastly increased.  $\beta$  depends to a high extent on the radius of the particles which appears in the third power.

The elegant theorist *H. Müller*, 1928 (288), transformed *M. v. Smoluchowski's* coagulation mechanics into vector analysis and thus attained still further generality. Some of *Müller's* considerations on streaming coagulation are mentioned in the following.

The migration of the centres of gravity of coagulating particles through the coagulation skin has in general two causes, *viz.* Brownian movements (diffusion) and the action of external forces upon the particles (gravity, centrifugal force).

If the number of particles at a given point and at a given time is  $N$ , *Fick's* law gives the number of particles which migrate across the surface element  $d\sigma$ ,

$$\delta N_D = D \frac{\delta N}{\delta n} d\sigma dt, \quad (56)$$

where  $\frac{\delta N}{\delta n}$  is the gradient of the number of particles in the direction of the normal to the surface element. The exterior forces produce a movement of the particles or — what is the same — a flow of liquid relative to the particles. Since we assume this streaming to be stationary, *i. e.* independent of time, it may be described by a vector field  $\underline{v}(x, y, z, 0)$ . This streaming is identical with *Stokes' hydrodynamic* frictional flow around the nucleus of coagulation.

As a consequence of the incompressibility equation,

$$\operatorname{div} \underline{v} = 0. \quad (57)$$

The number of particles carried through the surface element  $d\sigma$  by the flow is thus

$$\delta N_s = N v_n d\sigma dt, \quad (58)$$

where  $v_n$  is the vector component of the rate of flow in the direction of the normal to the surface element.

When these considerations are employed for the total coagulation skin  $\sigma$  by extending the surface integral over the total surface, we obtain the number of coagulated particles during the time interval  $dt$

$$\delta N = \int_{\sigma} \left( D \frac{\delta N}{\delta n} + N v_n \right) d\sigma dt. \quad (59)$$

On the coagulation skin,  $N$  is constant equal to zero, and  $\frac{\delta N}{\delta n}$  equal to the total gradient of  $N$ . Equation (59) is then reduced to

$$\delta N = \int_{\sigma} D \operatorname{grad} N d\sigma dt = 2 N_0 W dt, \quad (60)$$

since the coagulation probability, *i. e.* the coagulated quantity per second, is

$$W = \frac{1}{2 N_0} \int_{\sigma} D \operatorname{grad} N d\sigma. \quad (61)$$

In order to obtain the coagulation probability it is sufficient to determine  $\operatorname{grad} N$ , *i. e.* the particle distribution around the nucleus during coagulation.

If the same considerations hold in the case of an arbitrary volume, the enclosing surface of which replaces  $\sigma$ , and Gauss' integration rule often denoted as the divergence theorem is applied to equation (59)\*), we get

$$\frac{\delta N}{\delta t} = D \operatorname{div} \operatorname{grad} N + \operatorname{div} (N \underline{v}), \quad (62)$$

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\*) Thereby a surface integral is transformed into a volume integral.

or, since  $\text{div } \underline{v} = 0$ ,

$$\frac{\delta N}{\delta t} = D \text{ div grad } N + (\underline{v} \text{ grad } N). \quad (63)$$

According to *Smoluchowski*, the stationary particle distribution, only, is of significance for coagulation, and hence  $\frac{\delta N}{\delta t} = 0$ , and

$$D \text{ div grad } N + (\underline{v} \text{ grad } N) = 0. \quad (64)$$

For the determination of the solution of this differential equation we have the boundary conditions

$N_{(\sigma)} = 0$  on the coagulation skin  $\sigma$ .

$N_{\infty} = N_0$ , i. e. at a great distance from the nucleus of coagulation the latter is without any influence upon the number of particles.

We now mention only the main results of *H. Müller's* brilliant solution.

In the limit cases

$v = 0$  we have ordinary coagulation,

$r_p = 0$  the radii of the small micelles are negligible compared with those of the nuclei of coagulation, the streaming effect becomes zero.

Let us assume the nucleus of coagulation to be at rest and the colloid to flow with a velocity  $v$ . The coagulation skin of the nucleus has a radius  $a = R_p + r_p$ , if  $R_p$  and  $r_p$  are the radii of the nucleus and the small micelles, respectively.

On the coagulation skin we get

$$(\text{grad } N)_{\rho=a} = \frac{N_0}{a} e^{-C \cos \theta}, \quad (65)$$

where  $\theta$  is the azimuth to the direction of flow,  $D$  the mutual diffusion constant

$$D = \frac{k\Theta}{6\pi\eta} \left( \frac{1}{R_p} + \frac{1}{r_p} \right) \quad (66)$$

of the nucleus and a small particle, and

$$C = \frac{v}{D} \left[ a - R_p \left( \frac{3}{2} \ln \frac{a}{R_p} + \frac{1}{4} \frac{R_p^2}{a^2} + \frac{3}{4} \right) \right]. \quad (67)$$

The number of coagulated particles is thus greater on the counter-streaming side than on the reverse of the nucleus of coagulation. We get for the coagulation probability

$$\delta W = 2 \pi D a^2 \int_0^\pi \text{grad } N_{(r=a)} \sin \theta d\theta \quad (68)$$

$$W = 4 \pi N_0 D a \frac{\sinh C}{C} \quad (\sinh = \text{hyperbolic sine}). \quad (69)$$

Since  $4 \pi N_0 D a$  is the coagulation probability of the attachment of a particle to a resting nucleus, the probability for its adherence to a nucleus streaming with a velocity  $v$  is increased by a factor

$$F = \frac{\sinh C}{C}, \quad (70)$$

where  $C$  has the above mentioned meaning.

When also coagulating small micelles participate in the streaming,  $v$  signifies the relative velocity; if this is zero, as in a monodispersive system,  $C$  becomes zero and the factor  $F = 1$ . Hence, in a monodispersive system, we should not find any influence of streaming; in polydispersive systems with a great factor  $F$ , however, the effect of streaming is considerable.

During sedimentation and during stirring (centrifuging), the rate of flow of the particles is proportional to their mass ( $m$ ); in the case of spherical particles with a mass density  $s$ , we get

$$m = \frac{4}{3} \pi R_p^3 s \quad (71)$$

and the force

$$K = m j, \quad (72)$$

where  $j = g$  for sedimentation, and

$j = d w^2$  for centrifuging ( $d$  = distance from the centre of rotation,  $w$  = velocity at this distance).

The effect of streaming can just be proved experimentally for  $C \geq 0.8$ . When  $C = 2.1$ , coagulation is doubled by the streaming, and when  $C = 5$ , ordinary coagulation can be disregarded compared with the enormous effect of streaming.

At a given radius of the nucleus, the influence of streaming reaches a maximum when the radius of the particles carried along is 0.8 times that of the nucleus. The greater the nucleus of

coagulation, the greater the effect of streaming; however, the influence is bound to small micelles, the radius of which is

$$r_p \geq \sqrt{\frac{1.2 k \Theta}{\pi j s}} \quad (73)$$

( $k$  is the Boltzmann constant); minor particles remain in suspension.

*H. Müller's* theoretical results are in agreement with *P. Tuorila's* experiments (422).

### § 31. RAPID COAGULATION OF SYSTEMS WITH NON-SPHERICAL PARTICLES. (ROD- AND LEAF MICELLES).

In his previously mentioned generalization of *Smoluchowski's* coagulation theory, *H. Müller*, 1928 (288), succeeded in giving a theory of the coagulation of non-spherical particles.

Where the effect of exterior forces upon coagulation can be disregarded, the relative velocity of the particles becomes zero, so that the general differential equation of the coagulation problem is reduced to the well-known *Laplace's* equation

$$\operatorname{div} \operatorname{grad} N = 0 \quad (74)$$

with the boundary conditions

$$N_\sigma = 0 \text{ and } N_\infty = N_0. \quad (75)$$

If we set

$$N = \Phi - N_0 \quad (76)$$

we must also get

$$\operatorname{div} \operatorname{grad} \Phi = 0. \quad (77)$$

The boundary conditions for  $\Phi$  become

$$\Phi_\sigma = -N_0 \quad \Phi = 0. \quad (78)$$

The determination of  $\Phi$  is now analogous to the fundamental problem of electrostatics, *viz.* the determination of the potential distribution around a charged surface ( $\sigma$ ) of a conductor (to the potential  $-N_0$ ). On the basis of this analogy, we may immediately conclude that during coagulation the micelles mainly adhere to another micelle, where the geometrical curvature of the surface is great.

If  $C$  denotes the electrostatic capacity of the coagulation skin, and  $D_{rel}$  the relative diffusion coefficient of the particles, the coagulation probability becomes

$$W = 2 \pi D_{rel} C. \quad (79)$$

Since the capacity of a sphere is equal to its radius, we get for *Smoluchowski's* case

$$W_0 = \frac{4}{3} \frac{k \Theta}{\eta}. \quad (80)$$

The equivalent radius (*cf.* p. 51) of the nucleus of coagulation be  $R_p$  and that of the coagulating particle be  $r_p$ , the relative diffusion coefficient may be expressed as

$$D_{rel} = \frac{k \Theta}{6 \pi \eta} \left( \frac{1}{r_p} + \frac{1}{R_p} \right), \quad (81)$$

so that the coagulation probability is

$$W = \frac{4}{3} \frac{k \Theta}{\eta} \frac{R_p + r_p}{4 R_p r_p} C = \gamma W_0. \quad (82)$$

$\gamma$ , which is termed the form constant, corresponds to half the ratio attraction radius : particle radius in *Smoluchowski's* theory ( $\gamma = \frac{1}{2} \frac{R}{r_p}$ ).

In the case of very long rod micelles which may be considered degenerated ellipsoids of revolution the form factor becomes equal to  $\ln 2a/b$ , where  $a$  and  $b$  are the semi-axes of the ellipsoid. In very thin circular sheets, this factor lies between 1 and 1.5, *i. e.* the coagulation probability of non-spherical particles is always greater than that of spherical particles.

Due to the slight deviations of the coagulation course in the case of leaf micelles, these will coagulate approximately according to *Smoluchowski* (in monodispersive suspensions), while considerable deviations must be expected in rod suspensions. When investigating stored sols of Benzopurpurin and vanadium pentoxide, the particles of which were long rods, *G. Wiegner* and *C. E. Marshall*, 1929 (448), obtained values of up to 100 of the ratio  $\frac{R}{r_p}$ . Due to the clumsy shape of secondary particles compared with the shape of the primary particles, the ratio  $\frac{R}{r_p}$

decreases rapidly towards the value 2 in the course of the experiment. A further proof of the influence of the rod shape upon rapid coagulation was found in the measurements of freshly prepared sols which contained very short, almost spherical particles and which coagulated as was to be expected from *Smoluchowski's* theory with  $\frac{R}{r_p}$ -values between 2 and 2.4.

The fact that clay sols presumably containing leaf micelles coagulate according to *Smoluchowski's* theory is also in favour of *Müller's* theory (288).

## § 32. THE APPLICATION OF COAGULATION MEASUREMENTS TO SUSPENSIONS OF BLOOD CORPUSCLES.

The most important principles of measuring coagulation are outlined in brief in § 24 (p. 63).

### *Direct methods.*

1. An analysis of intercorpuscular forces has until now not been applied. The author's own investigations will be discussed later (pp. 106 and 169).

### 2. Counting method.

*E. Ponder*, 1926 (333), was the first to try the application of *Zsigmondy-Smoluchowski's* counting method to the quantitative measurement of the "rouleaux formation" of blood corpuscles. Technique: The corpuscles were centrifuged from oxalate blood, and by means of a pipette the plasma was translocated into a glass placed in a thermostat. From the ear of the donor, a given small amount of blood was taken by means of a capillary pipette and was added to the plasma in the glass. The mixing tubes were moved during the experiment "as one shakes a boiling tube".

At a well-defined moment, a drop of the mixture was placed on a slide and was covered with a coverglass smeared with vaseline at the edges in order to inhibit streaming and evaporation. In this thin layer of liquid the blood corpuscles sedimented rapidly so that the aggregation process ceased. Then, 20–30 microphotographs, usually under a magnification of about 300 times, were taken of every preparation. On the ready preparations which were studied under a microscope with low magnification

a counting of single-, double-, triple-, *etc.* particles was performed.

*Ponder* found the radius of action to be the greater, the more rapidly "rouleaux formation" occurred. During the course of the single experiments, however, it seemed not necessary to assume any variation of the radius of action ( $R$ ). The magnitude of the radius of action which could vary considerably depended on the corpuscle concentration, the temperature, and "such undefined factors as the charge of the cells and the state of red cell surface".

It is a great pity that *Ponder's* paper contains neither any figures of  $R$  nor of the variation of  $R$  with the concentration or the temperature, nor any information whether *Smoluchowski's* theory is fulfilled in these respects.

The "rouleaux formation" varied symbatically with the temperature so that aggregation occurred more slowly at lower temperature (15°C) and more rapidly at higher temperature (37°C).

*J. Oliver* and *P. Smith*, 1926 (312), investigated suspensions of red blood corpuscles in isotonic saccharose solutions to which a little sodium hydroxide was added as a stabilizer (until the solution was M/500). The suspension was brought to "rapid" coagulation by addition of aluminum trichloride (until the solution was M/4000). For the counting, *Zsigmondy's* "Schutzkolloid-methode" was employed, where the samples were taken in intervals, and a 1 per cent gelatine solution was added. Then, the number of particles ( $\Sigma v$ ,  $v_1$  and  $v_2$ ) was determined by counting in an ordinary haemacytometer or counting chamber for haematologic purposes.

The radius of action was rather constant within the single experiments, and the calculated number of single particles was in good agreement with the number really found; furthermore, the number of double particles was calculated and compared with the number found experimentally. *Smoluchowski's* ratio (radius of action : radius of particles)  $\frac{R}{r}$  varied enormously in different experiments (from 142.3 to 2513). In spite of low concentrations, the rate of agglutination was found to be of the same order of magnitude as in concentrated colloidal solutions. The peculiarities



of the studied system became evident when compared with a gold sol.

The volume of the blood corpuscles was 50 000 times greater than that of the gold particles, and their Brownian movements were very small. Since the blood corpuscles really formed aggregations in spite of the fact that the mean distance between the particles was greater than in the gold sol which coagulated at the same rate, we must assume an unknown factor causing this phenomenon.

### *Indirect methods.*

For a measurement of the coagulation rate of concentrated blood corpuscle suspensions, such as natural blood, we must resort to indirect physical methods, since the counting method is unfeasible in these cases.

In general, coagulation is an undesired phenomenon disturbing the sedimentation analysis; variations of the sedimentation velocity, however, may serve as a measure of the ability to aggregate (simple sedimentation experiments); this is the case with blood sinking. The principle of this method has already been mentioned in the description of the temporal course of blood sinking (*cf.* the shape of the curve of the blood sinking reaction, p. 44). The application of the real sedimentation analysis will be described below, in connection with "optical methods".

#### 1. *Optical methods.*

When light passes a suspension of blood corpuscles the intensity decreases due to scattering by the corpuscles and to a smaller extent due to absorption in the corpuscle haemoglobin or in the plasma.

The theoretico-physical calculation of dispersion in suspensions of spherical and ellipsoidal particles which are small compared with the wave-length of the light is a frequently treated problem. (For further literature, *cf.* *H. Freundlich*, 1932 (125, II, pp. 27 and 31), and *Ph. Frank and R. v. Mises*, 1935 (121, II, pp. 871 and 875). However, calculations of corresponding problems with large particles are lacking completely. The dispersion of light in suspensions of relatively large particles (such as blood corpuscle suspensions) should be treated by means of mathematical ana-

logies known from the transmission of radio waves around the globe (*Ph. Frank and R. v. Mises* (121, II, p. 963)).

In nephelometric measurements during blood sedimentation, *A. Aggazotti and C. Manzini*, 1929 (14), and *A. Aggazotti and G. Bucciardi*, 1930 (13), found a reduced dispersion (white light) during the first phase of the sinking reaction; they regarded the erythrocyte aggregation as the cause of this phenomenon.

When applying a photoelectric method to the determination of the blood corpuscle concentration during "Schlämmanalyse" of the blood, *B. Swedin*, 1936 (407) and 1938 (408), found an apparent decrease in concentration in the beginning of the blood sedimentation. *Swedin* assumed that both aggregation and sedimentation in the arising polydispersive suspension must be responsible for the reduced light dispersion.

*B. Swedin (loc. cit.)* investigated, furthermore, the absorption of light in corpuscle suspensions with varying content of tragacanth and he was able to prove that the absorption was least in suspensions showing the highest degree of aggregation. Finally, it should be mentioned that *S. L. Ørskov*, 1935 (461), observed a reduced dispersion in dilute monodispersive blood corpuscle suspensions at a slight volume increase of the corpuscles.

## 2. Viscosity measurements.

It is not reliably known how far erythrocyte aggregations change the viscosity of blood corpuscle suspensions. According to *A. Einstein's* viscosity formula (96, 98), a change in viscosity due to aggregation should not be expected. Since, however, this process seems to be accompanied by an inclusion in the corpuscle conglomerates of smaller amounts of plasma, *i. e.* an increase in volume concentration of the disperse phase, an increased viscosity cannot be excluded. In this connection, we may recall *L. Berczeller and H. Wastl's* observations (29) of the reduced time of passage when blood streamed repeatedly through a pipette, a phenomenon which may hardly be explained in any other way.

Since the dispersion degree of the red cells may easily be changed by minimum influences, viscosity measurements are hardly suited for the study of the aggregation process.

### 3. Measurement of the electric conductivity of the suspension.

Conductivity measurements often enable us to follow the course of coagulation of lyophobic colloids. It is assumed that an ion exchange which has the character of a complete double decomposition occurs between the suspension medium and the disperse phase and causes the variations in conductivity. The coagulated particles absorb different ions from the suspension fluid and give off equivalent amounts of other ions of the same sign. (As regards the extensive literature, references will be found in the manuals of colloidal chemistry, for instance in *H. Freundlich*, 1932 (125, II, p. 132)).

The colloidal particle with its compensating ions is often denoted as "micelle". The ions which neutralize the charge of the particle are called "Gegenionen" (counter ions). According to *G. Wiegner*, 1930 (447), the binding of the "counter ions" to the micelles appears in the so-called "suspension effect" which means that the suspension reacts either more acid or more alkaline than the corresponding medium. This phenomenon originally studied on suspensions of earth, only, seems to be generally valid for all colloidal systems.

*H. R. Christensen* and *S. Touborg Jensen*, 1924 (65), proved that the  $p_H$  of earth suspensions often deviated markedly from the  $p_H$  of the corresponding filtrates. In the case of acid earths, the suspensions showed more acid  $p_H$  values than the filtrates, while the opposite was found on alkaline earths. *E. Billmann* and *S. Touborg Jensen*, 1927 (35), observed that the difference in reaction between suspension and filtrate increased with increasing content of earth in the suspension.

*G. Wiegner's* pupil, *H. Pallmann*, 1930 (322), who performed comprehensive investigations of the suspension effect of a number of well-known colloids, mentioned still further references from this field. *Pallmann* came to the result that, up to moderate concentrations, the apparent  $p_H$  of the suspensions was proportional to the concentration. At still higher concentration, a depression of the effect could be noticed. On the same substance, the suspension effect increased with the degree of dispersion.

According to *A. Unmack's* careful testing, 1933 (425), the above mentioned differences in reaction must originate from one

or numerous sources of error involved in the experimental procedure.

*K. A. Hasselbalch* and *C. Lundsgaard*, 1912 (179), and *K. A. Hasselbalch*, 1917 (178), found increasing acidity of the sequence plasma — blood — concentrated corpuscle suspension (in plasma), as confirmed later by *I. M. de Corral y Garcia*, 1914 (69). *T. R. Parsons*, 1917 (324), did not succeed in proving any difference in reaction between blood and corresponding plasma; also *K. A. Hasselbalch* and *E. J. Warburg*, 1918 (180), were unable to detect any suspension effect (*cf. E. J. Warburg*, 1922 (432, p. 222) ).

Since conductivity measurements have not been applied earlier to the investigation of the aggregation rate of erythrocytes — disregarded the fact that certain conducting properties of moved, stirred, or streaming blood seem to be connected with the aggregation velocity — such measurements were carried out by the author (*cf. p. 171*). For this reason, the scarce literature from this field will be discussed here.

The effect of stirring of the blood upon the result of conductivity measurements on blood was first observed by *M. Oker-Blom*, 1900 (309), who made use of *S. Arrhenius'* model of conductivity cells in which the electrodes were placed horizontally one above the other. *Oker-Blom* stated that the conductivity increased when the blood column was too low. When the blood just reached the upper electrode, a layer poor in corpuscles was formed directly below the electrode — obviously due to sedimentation. Moreover, some of the blood corpuscles present between the electrodes in the beginning of the experiment sank below the lower electrode, so that the concentration of blood corpuscles in the measured column decreased.

*P. Fraenkel*, 1904 (120), recommended careful stirring for the measurement of the electric conductivity of the blood. At lacking or insufficient stirring, the true minimum was not always shifted in the same direction due to the sedimentation of erythrocytes, so that the conductivity was measured sometimes higher, sometimes lower than the "true" one. The initial state was reached very soon after stirring but, in blood with rapid sinking, such as horse blood, it could not be preserved even for a rather short time.

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this effect which he considered produced by colloid absorption by means of a special conductivity cell in which the electrodes were surrounded by 0.85 per cent sodium chloride solution and separated from the blood by cellophane membranes. When using these improved cells, the first phenomenon was nevertheless observed as soon as stirring was interrupted.

*E. Sigman, A. Kolin, L. N. Katz and K. Jochim, 1937 (378),* studied the conductivity of streaming blood (a. c. 1000 cycles per sec.). Defibrinated ox blood streamed from a container, where it was stirred now and then, through a long glass tube provided with platinum electrodes at both ends. These authors found two opposite effects, a tendency to increasing resistance dominating at slow streaming ("electrode effect") which was gradually overshadowed by a fall of resistance with increasing velocity of streaming ("flow effect"). The first mentioned was denoted as "electrode effect" because it disappeared when the electrodes were placed into standing blood or into salt solution in side arms of the streaming tube; the "flow effect", however, was uninfluenced by these manipulations.

The decrease in resistance was not quite proportional to the rate of flow but approached a limit value at rapid streaming. The "flow effect" was increased with increasing concentration of blood corpuscles, however, not linearly. Furthermore, a change in the ion concentration of the suspension medium was of some influence upon the "flow effect" which disappeared with haemolysis. It was remarkable that the "flow effect" at a given high rate of flow was less in samples with a great "electrode effect" than in samples with a small "electrode effect". The investigators were unable to give any explanation of this "electrode effect".

On the assumption that the "flow effect" is due to a "declumping action", the mentioned authors studied blood samples to which serum of different species was added and they found a smaller "flow effect" in these samples than in control samples without specific agglutination. The reduced "flow effect" was explained by the greater stability of agglutination conglomerates compared with that of rouleaux formation. By measurements of the conductivity across the blood stream, it could be excluded that the "flow effect" originated from an orientation of the corpuscles due to streaming, *i. e.* with a long axis parallel to the direction

of flow. Due to the great bore of the tube, the streaming was turbulent and an orientation was impossible.

Finally, conductivity phenomena in streaming blood were observed by *G. Achard*, 1938 (11, 12). While bearing in mind the disagreement between determinations of the blood corpuscle volume by centrifuging and by measurements of the electric conductivity, *A. Slawinski* and coworkers (*A. Slawinski* and *J. Pakowski*, 1930 (380), *F. Labendzinski* and *A. Slawinski*, 1931 (239)) developed a new method in which the conductivity of the corpuscle sediment was measured instead of the instable conductivity of the fully dispersed suspension. These investigators found that erythrocyte aggregation increased the resistance of the sediment. According to *A. Slawinski*, the instability of the conductivity of corpuscle suspensions is caused by orientation and precipitation of the erythrocytes.

#### *4. Measurement of the aggregation by means of specific gravity estimations of the suspension or direct weighing of the sediment.*

These methods which are frequently applied in "Schlämmanalyse" (*S. Odén*, 1915 (302) and 1920 (304), *H. Gessner*, 1926 (150) and 1931 (151)) are unsuited in the case of blood corpuscle suspensions (*K. Stöcklin*, 1926 (404)) due to the minute difference in specific gravity between particles and suspension fluid.

Section III.  
THE AUTHOR'S THEORETICAL  
INVESTIGATIONS.

§ 33. THE APPLICATION OF SMOLUCHOWSKI'S  
COAGULATION THEORY TO THE PROBLEM OF  
INTERCORPUSCULAR ATTRACTION\*).

*(An extension of Smoluchowski's theory, interpretation of the  
"action radius").*

Between the particles of a colloidal system, various forces are active which determine the degree of dispersion of the colloid. Our lack of knowledge concerning these forces inhibited the development of a useful coagulation theory until *M. v. Smoluchowski*, 1917 (387), made an attempt to ascribe to the colloidal particles a given attraction space measured by the so-called action radius (*cf.* § 27, p. 67). In this way, *Smoluchowski* successfully avoided the problem of an internal mechanism of attraction forces, since now not the magnitude and distribution of these forces but only the sphere of their action was the decisive factor. According to *Smoluchowski*, the solution of this special problem is reserved for coming theories concerning the structure of the electric double layer.

*Smoluchowski's* simplified interpretation of the intercorpuseular forces — the assumption of an action radius corresponding to a constant force within the range of the sphere of action, a sphere with the radius  $R$ , and the complete lack of forces outside this sphere — is too idealized as to represent completely the true situation. The forces between the colloidal particles must vary continuously with the distance and they cannot be assumed to be exclusively repulsive or exclusively attractive; there is also

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\*) The results of the investigations discussed in this paragraph were published previously (*J. E. Thygesen*, 1939 (415)).



a possibility that attraction exists at one distance and repulsion at another distance.

In order to analyze the attraction radius more thoroughly, the author has made an attempt to generalize *Smoluchowski's* theory so that the theory comprises arbitrary intercorpuseular forces of attraction. It was, furthermore, investigated whether by means of such a general theory these forces can be determined physically on the basis of coagulation-kinetic experiments. While *Smoluchowski* assumed that the Brownian movements of the particles, only, determine the frequency of collisions (condition 4), p. 68), the forces assumed in our new theory imply an additional convection.

Since a diffusion process is merely a superposition of Brownian movements of individual particles, these movements may be calculated by solving a corresponding diffusion problem. We deduce the differential equation of the present case. Dealing with an external force, the density of current  $\underline{i}$  consists of two components, one of which,  $\underline{i}_D$ , is due to diffusion

$$\underline{i}_D = -D \text{grad } W, \quad (1)$$

while the other,  $\underline{i}_c$ , is due to convection

$$\underline{i}_c = W\beta \underline{f}, \quad (2)$$

$\beta$  being the hydrodynamic mobility of the particles (reciprocal resistance),  $D$  their diffusion coefficient,  $\underline{f}$  the vector of the external force, and  $W$  a partition function which, in the macroscopic case, is equal to the concentration.

For the total density of current, we get

$$\underline{i} = \underline{i}_D + \underline{i}_c = -D \text{grad } W + W\beta \underline{f}. \quad (3)$$

Since the divergence of the vector for the density of current is equal to the decrease in density of particles with time

$$\text{div } \underline{i} = -\frac{\partial W}{\partial t}, \quad (4)$$

we find (expressed in the form of vector analysis) the differential equation

$$\frac{\partial W}{\partial t} = D \Delta W - \beta \text{div } [W \cdot \underline{f}]; \quad (5)$$

the partition function  $W$  must satisfy this equation (5).

*Smoluchowski's* suppositions (except for 3) and 4), p. 68) may remain valid.

Instead of 3) we assume

8) that contact between particles is necessary for aggregation, *i. e.* the distance between the centres must be equal to the diameter of the particles.

For the sake of simplicity, we furthermore assume

9) a non-orientated coagulation, *i. e.* aggregation due to collision of particles, independent of the position of the particles *inter se*. The force  $\underline{f}$  will then only be a function of  $r$  (the distance from the centre of the condensation nucleus)

$$\underline{f} = \underline{f}(r), \quad (6)$$

so that the concentration  $W$  in the sphero-symmetrical system depends exclusively on  $r$

$$W = W(r). \quad (7)$$

Expressing the force vector  $\underline{f}$  in the usual way by means of a unit vector  $\frac{\underline{r}}{r}$  ( $\underline{r}$  radius vector), we get

$$\underline{f} = -f(r) \left( \frac{\underline{r}}{r} \right), \quad (8)$$

where  $f(r)$  is a positive value, when

10) the force is supposed to cause attraction.

*Smoluchowski's* analysis has shown that the stationary distribution of particles only determines the amount coagulated within a given time (supposition 6), p. 68). Hence, we look merely for a stationary solution of the above differential equation\*) which is thus reduced to

$$4a) \quad D \Delta W - \beta \operatorname{div} [W \cdot \underline{f}] = 0 \quad (9)$$

which replaces the condition

$$4) \quad D \Delta W = 0 \quad (10)$$

in *Smoluchowski's* theory.

According to well-known theorems from vector analysis, we get

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\*) Addendum: Cf. also *N. Fuchs*, *Z. Physik* 89, 736, 1934.

$$\operatorname{div} [W \cdot \underline{f}] = - \operatorname{div} \left[ \left( \frac{Wf}{r} \right) \cdot \underline{r} \right] = - \frac{Wf}{r} \operatorname{div} \underline{r} - \left( \operatorname{grad} \frac{Wf}{r}, \underline{r} \right) = -3 \frac{Wf}{r} - r \frac{d}{dr} \left( \frac{Wf}{r} \right). \quad (11)$$

By substitution of the expression obtained for

$$\operatorname{div} [W \cdot \underline{f}] \quad \text{and} \quad \Delta W = \frac{d^2 W}{dr^2} + \frac{2}{r} \frac{dW}{dr} \quad (12)$$

into the differential equation, we get

$$D \left\{ \frac{d^2 W}{dr^2} + \frac{2}{r} \frac{dW}{dr} \right\} + \beta \left\{ 3 \frac{Wf}{r} + r \frac{d}{dr} \left( \frac{Wf}{r} \right) \right\} = 0. \quad (13)$$

Since this may be written as

$$\frac{d}{dr} \left\{ r^2 \frac{dW}{dr} + \frac{\beta}{D} r^2 Wf \right\} = 0, \quad (14)$$

the integration with  $c_1$  as an arbitrary constant leads to

$$\frac{dW}{dr} + W \frac{\beta}{D} f(r) = \frac{c_1}{r^2}. \quad (15)$$

By further integration with  $c_2$  as a new arbitrary constant we get

$$W = e^{-\frac{\beta}{D} \int_{r_0}^r f(r) dr} \left\{ \int_{r_0}^r \frac{c_1}{r^2} e^{+\frac{\beta}{D} \int_{r_0}^r f(r) dr} dr + c_2 \right\}. \quad (16)$$

For the determination of the constants  $c_1$  and  $c_2$  the initial conditions are

$W = 0$  for  $r = r_0$  (contact), and

$W = c$  (the constant initial concentration) for  $r \rightarrow \infty$ .  $c_2 = 0$  satisfies the first condition. Setting

$$A(\infty) = \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr \quad (17)$$

which is constant, we get

$$c_1 = \frac{c}{e^{-A(\infty)} \int_{r_0}^{\infty} \frac{e^{+A(\infty)}}{r^2} dr}. \quad (18)$$

By substitution of the constants  $c_1$  and  $c_2$ , we then obtain

$$W = c e^{-[A(r) - A(\infty)]} \frac{\int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr}{\int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr}. \quad (19)$$

( $W = c$  satisfied for  $r = \infty$ ), where

$$A(r) = \frac{\beta}{D} \int_{r_0}^r f(r) dr. \quad (20)$$

For  $r_0 = R$  (action radius) and  $f(r) = 0$  for  $r > R$  and large  $t$  (stationary state), the formula found for  $W$  becomes *Smoluchowski's* formula, since  $A(r) = 0$  for all  $r \geq r_0$ .

$$W = c \frac{\int_{r_0}^r \frac{1}{r^2} dr}{\int_{r_0}^{\infty} \frac{1}{r^2} dr} = c \frac{\left| -\frac{1}{r} \right|_R^r}{\left| -\frac{1}{r} \right|_R^{\infty}} = c \left\{ 1 - \frac{R}{r} \right\}. \quad (21)$$

For the determination of the in-diffusing amount of substance we calculate

$$\frac{\partial W}{\partial r} = \frac{c e^{+A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr} \frac{d}{dr} \left\{ e^{-A(r)} \int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr \right\} =$$

$$\int_{r_0}^{\infty} \frac{c e^{+A(\infty)}}{r^2} dr \left\{ \frac{1}{r^2} - \frac{\beta}{D} f(r) e^{-A(r)} \int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr \right\}, \quad (22)$$

the first factor being a constant. For  $r = r_0$  we get

$$\left. \frac{\partial W}{\partial r} \right|_{r=r_0} = c \frac{1}{r_0^2} \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr}. \quad (23)$$

The amount diffusing across the sphere of contact (radius  $r_0$ ) per second will thus be

$$4 \pi r_0^2 D \left. \frac{\partial W}{\partial r} \right|_{r=r_0} = 4 \pi D c \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr}, \quad (24)$$

and *Smoluchowski's* action radius is

$$R = \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr}. \quad (25)$$

By integration by parts, the integral in the denominator may be transformed into

$$\begin{aligned} \int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr &= -\frac{1}{r} e^{A(r)} \Big|_{r_0}^{\infty} + \int_{r_0}^{\infty} \frac{1}{r} e^{A(r)} \frac{\beta}{D} f(r) dr \\ &= \frac{1}{r_0} \left\{ 1 + r_0 \int_{r_0}^{\infty} \frac{1}{r} e^{A(r)} \frac{\beta}{D} f(r) dr \right\}. \end{aligned} \quad (26)$$

Assuming small forces and evolving after  $f(r)$ , we get

$$e^{A(\infty)} = 1 + A(\infty) + \dots \quad \text{and} \quad e^{A(r)} = 1 + A(r) + \dots \quad (27)$$

whereafter

$$R = r_0 \frac{1 + A(\infty) + \dots}{1 + \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} (1 + \dots) dr} \quad (28)$$

so that, when employing the well-known formula

$$\frac{1}{1+x} = 1 - x + \dots, \quad (29)$$

we obtain

$$R = r_0 \left( 1 + \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr \right) \left( 1 - \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} dr \right). \quad (30)$$

By the usual discarding of the product term

$$- \left( \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr \right) \left( \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} dr \right) \quad (31)$$

we finally get

$$R = r_0 \left\{ 1 + \frac{\beta}{D} \int_{r_0}^{\infty} f(r) \frac{r - r_0}{r} dr \right\} = r_0 (1 + \text{constant}) = \text{constant}. \quad (32)$$

For  $f(r) = 0$  and  $r_0 = 2 r_p$  ( $r_p$  radius of the particle) *Smoluchowski's* ratio  $\frac{R}{r_p} = 2$ .

If distance forces are active, *i. e.*  $f(r) > 0$ , we obtain a constant action radius greater than  $2 r_p$ .

Since the action radius is constant, all *Smoluchowski's* formulas for the calculation of the number of particles remain valid. This may explain why *Smoluchowski's* theory satisfactorily describes the coagulation of hydrophobic colloids, although the rough assumption of a simple attraction sphere undoubtedly fails to give a correct description of the forces between the particles.

According to the formula found for  $R$ , the action radius must be a function of the absolute temperature  $\theta$ . Only if intercorporeal forces are independent of the temperature, it becomes possible to calculate  $f(r)$  from  $R$ , which even enters implicitly the equation in form of an integral.

By transcription of the formula for  $R$  we get

$$R = \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr} = \frac{1}{\int_{r_0}^{\infty} \frac{e^{A(r) - A(\infty)}}{r^2} dr} = \frac{1}{\int_{r_0}^{\infty} \frac{e^{-\frac{\beta}{D} \int_r^{\infty} f(r) dr}}{r^2} dr}, \quad (33)$$

since

$$A(r) - A(\infty) = \frac{\beta}{D} \left\{ \int_{r_0}^r f(r) dr - \int_{r_0}^{\infty} f(r) dr \right\} = -\frac{\beta}{D} \int_r^{\infty} f(r) dr = -\frac{M}{k\theta}. \quad (34)$$

$M$  is an abbreviated notation for the integral with the limits  $r$  and  $\infty$ . The value for  $\frac{\beta}{D}$  is derived from

$$D = \frac{H\theta}{N} \frac{1}{6\pi\eta r_p} = k\theta\beta. \quad (35)$$

$H$  stands for the gas constant,  $\theta$  for the absolute temperature,  $N$  is *Avogadro-Loschmidt's* figure,  $\eta$  the coefficient of internal friction,  $r_p$  the particle radius, and  $k$  *Boltzmann's* entropy constant.

The integral  $M$  is zero when  $r$  is greater than the range of the forces. The quantity  $\frac{M}{k\theta}$  being positive, we get by expansion of the  $e$  power in a *Maclaurin* series and by integration term by term

$$\frac{1}{R(\theta)} = \int_{r_0}^{\infty} \frac{e^{-\frac{M}{k\theta}}}{r^2} dr = \int_{r_0}^{\infty} \frac{\sum_{n=0}^{\infty} \frac{1}{n!} \left(-\frac{M}{k\theta}\right)^n \frac{1}{\theta^n}}{r^2} dr = \sum_{n=0}^{\infty} A_n \frac{1}{\theta^n}, \quad (36)$$

where  $A_n$  signifies the constant coefficients of the new series. By measuring  $R$  as a function of the temperature, the  $A$ 's may be determined and, thus, some information about  $R$  may be obtained.

If the force function  $f(r)$  is known, the action radius may be calculated. If the attraction takes place according to the function

$$f(r) = a \frac{1}{r^2} \quad (37)$$

the corresponding action radius may be calculated from

$$-\frac{a}{k\theta} \int_r^{\infty} \frac{1}{r'^2} dr' = -\frac{a}{k\theta} \left[ -\frac{1}{r'} \right]_r^{\infty} = -\frac{a}{k\theta} \frac{1}{r} \quad (38)$$

$$\int_{r_0}^{\infty} \frac{e^{-\frac{a}{k\theta} \frac{1}{r'}}}{r'^2} dr' = - \int_{\frac{1}{r_0}}^0 e^{-\frac{a}{k\theta} r'} dr' = \frac{k\theta}{a} \left( 1 - e^{-\frac{a}{k\theta} \frac{1}{r_0}} \right) \quad (39)$$

---

\*) Where the dimension  $\left[ \frac{\text{cm}^3 \text{ gram}}{\text{sec}^2} \right]$  is given to the proportionality constant, i.e. a force must have the dimension  $\left[ \frac{\text{gram cm}}{\text{sec}^2} \right]$ .

as we introduce  $r' = \frac{1}{r}$  as a new variable, *i. e.*

$$R = \frac{a}{k\theta \left(1 - e^{-\frac{a}{k\theta} \frac{1}{r_0}}\right)} = \frac{a}{k\theta} \quad (40)$$

since  $\frac{a}{k\theta} \frac{1}{r_0}$  is always large.

In this simple case ("square law"),  $R$  and  $\theta$  will be inversely proportional, *i. e.*, the reciprocal coagulation time  $\frac{1}{T}$  is proportional to the fluidity of the suspension medium  $\frac{1}{\eta}$ , since

$$\frac{1}{T} = 4\pi DR\nu_0 \text{ and } D = k\theta \frac{1}{6\pi\eta r_p}. \quad (41)$$

In *Smoluchowski's* case — no distance forces —  $R$  is constant, and  $\frac{1}{T}$  is proportional to  $\theta \cdot \frac{1}{\eta}$ . In both cases,  $\frac{1}{T}$  increases with temperature, however, it increases more rapidly in *Smoluchowski's* case.

If the force itself depends upon temperature,  $f(r)$  cannot be calculated from  $R(\theta)$ ;  $f(r)$  at a definite temperature as well as the variation of  $f(r)$  with temperature may thus be determined by the following direct method.

The constant action radius (*Smoluchowski's* ratio  $\frac{R}{r_p} = 2$ ) in systems with short-range intercorpuseular forces need not necessarily express the independency of these forces of the temperature, as considerable changes in strength do not alter the rate of coagulation, if only the forces are so great that each collision of particles results in aggregation ("rapid" coagulation).

#### § 34. METHOD OF DIRECT DETERMINATION OF INTER-CORPUSCULAR FORCES.

In spite of the fact that blood corpuscles due to their enormous size compared with that of the particles of ordinary hydrophobic colloids show only slight Brownian movements, the author was able to observe "rouleaux formation" in fresh corpuscle-plasma suspensions under the microscope after the lapse of a relatively



short time and even in rather dilute suspensions (*cf.* below, p. 163).

While very short-range forces cause coagulation of most (hydrophobic) colloidal solutions, the direct effect of long-range intercorpuseular forces may be observed which contribute to "rouleaux formation" of the blood corpuscles (*cf.* p. 164).

With the hope of being able to study the mechanism of erythrocyte aggregation by means of a determination of these forces (*cf.* an ideal measurement of coagulation mentioned on p. 63), the author has developed a theory of direct measurement of forces based upon kinematographic records of the particle movements.

Together with the general coagulation theory (*cf.* p. 72), Smoluchowski's ratio  $\left(\frac{R}{r_p}\right)$  between action radius and particle radius which represents a coarse approximation of coagulation forces was discussed in detail.

Since  $\frac{R}{r_p} > 2$  may appear in two essentially different ways, it seems useful to classify the (hydrophobic) colloidal systems in two groups, *viz.*

#### I. Systems with short-range intercorpuseular forces:

$$\frac{R}{r_p} \leq 2 \text{ and}$$

$$\frac{R}{r_p} > 2 \text{ due to size (a) and form (b) of the particles;}$$

- (a) polydispersive suspensions of spheres showing a Wiegner-Galecki effect,
- (b) monodispersive systems, the particles of which deviate from the spherical shape (rod- or leaf micelles).

#### II. Systems with far-range intercorpuseular forces:

$$\text{all other cases with } \frac{R}{r_p} \gg 2.$$

Very short-range forces — considered under I — which are only effective when the particles touch each other will not cause accelerated coagulation, not even at enormously increased forces. Long-range intermicellar forces, however, may accelerate coagulation, since their increase must cause a particle convection which

must be superposed the diffusion towards the nuclei of coagulation. This phenomenon is especially marked in suspensions of large particles (dispersoids), the diffusion coefficient of which is so low that the diffusion alone is not able to cause coagulation within a multiple of the actual coagulation time.

According to the author's opinion, not only different suspensions of erythrocytes, but also numerous other suspensions of cells (agglutinations of yeast cells, protozoes, and bacteria) may serve as examples for such systems.

When short-range coagulation forces are concerned (group I), the measurement of the adhesion of colloidal particles to the wall of the same material seems to provide us with some information. Among others, A. v. Buzagh, 1929/30 (57, 58, 59, 60), studied the adhesion of quartz particles to quartz walls by means of a "Haftzahl"- and an "Abreisswinkel"-method.

The author's direct measurements of forces, the principle of which will be described below, comprehends only group II.

We consider two equally large spherical particles, 1 and 2 (cf. Fig. 2), whose size and direction of the central line are determined by the vector  $\underline{r}$ .

If  $\underline{r}$  is expressed by the radius vectors  $\underline{x}_1$  and  $\underline{x}_2$  of the particles 1 and 2, we have

$$\underline{r} = \underline{x}_2 - \underline{x}_1 \quad (42)$$

Particle 1 is subject to the following forces:

a 1) the completely irregular influence of force  $\underline{X}_1$ , manifest in the Brownian movements of the particle.

b 1) the intercorpuseular attraction

$$\underline{f}_1 = f(r) \left( \frac{\underline{r}}{r} \right), \quad (43)$$

where  $\left( \frac{\underline{r}}{r} \right)$  is the unit vector, and  $f(r)$  the function of force in-

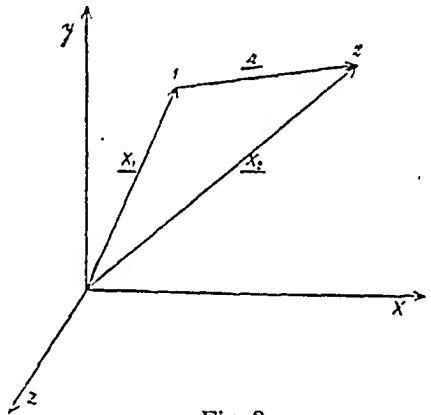


Fig. 2.  
The vector diagram represents the central line between particles 1 and 2 as a vector  $\underline{r}$  determined by the radius vectors  $\underline{x}_1$  and  $\underline{x}_2$ .

dicating the dependence of the force upon the position relative to the other particle.

c 1) a force of friction

$$-\gamma \frac{dx_1}{dt} \quad (44)$$

the magnitude of which is directly proportional to the velocity of the particle, and the direction of which is opposite to the direction of the movement of the particle;  $\gamma$  means the hydrodynamic resistance coefficient (or reciprocal mobility) which is the same for both particles.

Particle 2 is submitted to similar forces, *viz.*

a 2)  $\underline{X}_2$  which produces the Brownian movements.

b 2)  $\underline{f}_2$ , the intercorpuseular attraction which, according to the law of action and reaction, is equal to  $\underline{f}_1$  in the opposite direction, *i. e.*

$$\underline{f}_2 = -f(r) \left( \frac{r}{r} \right). \quad (45)$$

c 2) the force of friction

$$-\gamma \frac{dx_2}{dt}. \quad (46)$$

Employing the definition of force, *viz.* mass multiplied by acceleration, generally denoted as *Newton's second law*\*), we have for particle 1

$$m \frac{d^2 x_1}{dt^2} = -\gamma \frac{dx_1}{dt} + \underline{X}_1 + \underline{f}_1. \quad (47)$$

and for particle 2

$$m \frac{d^2 x_2}{dt^2} = -\gamma \frac{dx_2}{dt} + \underline{X}_2 + \underline{f}_2. \quad (48)$$

By subtraction, we get the equation for the relative movement of the particles,

$$m \frac{d^2 r}{dt^2} = -\gamma \frac{dr}{dt} + (\underline{X}_2 - \underline{X}_1) - 2f(r) \left( \frac{r}{r} \right). \quad (49)$$

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\*) Correct only for constant mass.

From a large number of observed pairs of particles (studied in so dilute a suspension that we can pick out pairs of particles lying sufficiently far from the other particles that the attraction of the latter may be left out of consideration) we select all those which have a distance of  $r$ , and then forming the mean values of acceleration and velocity, we obtain

$$m \overline{\frac{d^2 r}{dt^2}} \Big|_r = -\gamma \overline{\frac{dr}{dt}} \Big|_r - 2 f(r) \left( \frac{r}{r} \right). \quad (50)$$

$\overline{X_2 - X_1} = 0$ , since the relative movement, produced by the Brownian movements of the particles, is a new Brownian movement, *i. e.*, completely irregular.

By solving the equation with reference to  $f(r)$ , now disregarding the direction of the central line, we get

$$f(r) = -\frac{\gamma}{2} \overline{\frac{dr}{dt}} \Big|_r - \frac{m}{2} \overline{\frac{d^2 r}{dt^2}} \Big|_r. \quad (51)$$

Through direct observation by means of kinematographic records, the change in  $r$ ,  $\Delta r$  during a given small time unit  $\Delta t$ , is measured. The equation for  $f(r)$  is then

$$f(r) = -\frac{\gamma}{2} \overline{\frac{\Delta r}{\Delta t}} \Big|_r - \frac{m}{2} \overline{\frac{\Delta(\Delta r)}{\Delta t^2}} \Big|_r. \quad (52)$$

( $\Delta(\Delta r)$  means the change in the change of  $r$ ).

We can now disregard the acceleration term on account of its negligible magnitude. If no forces at all are acting between the particles,

$$\overline{\frac{\Delta r}{\Delta t}} \Big|_r = 0. \quad (53)$$

If forces are active between the particles, we get the value of  $f(r)$  for the central distance  $r$ ; when following the phenomenon with time, we obtain a complete picture of  $f(r)$ .

With the method here employed—averaging the displacements of numerous pairs of particles—we have eliminated the Brownian movements.

Finally, by calculation of

$$\int f(r) dr \quad (54)$$

and by the application of previous formulas, we are able to determine the action radius and to compare the calculated value with values obtained by ordinary coagulation-kinetic experiments.

### § 35. THE TRANSLATIONAL BROWNIAN MOVEMENTS OF ELLIPSOIDAL PARTICLES.

In the following, a formula for the Brownian movement of an ellipsoid of revolution is derived by simple calculations which agree with the corresponding formulas by *R. Gans*, 1928/29 (145, 146, 147), and *F. Perrin*, 1934/36 (328, 329), in their brilliant but rather complicated deductions.

We look for an expression of the mean squares of the projection of the displacements on a given direction, in analogy to the usually applied method of measuring the Brownian movements of spherical particles.

The centre of the ellipsoid be the origin of two rectangular coordinate systems,

- I. the mobile system whose axes  $X'$ ,  $Y'$ ,  $Z'$  overlap with the directions of the principal axes of the ellipsoid, and
- II. the fixed system  $X$ ,  $Y$ ,  $Z$ .

The unit vectors of the non-labelled and the labelled systems be termed  $\underline{i}$ ,  $\underline{j}$ ,  $\underline{k}$ , and  $\underline{i}'$ ,  $\underline{j}'$ ,  $\underline{k}'$ , respectively, and the 9 cosines of direction of the coordinate axes relative to one another will be determined by the products of two and two of these vectors. In order to obtain the transformation formulas of the coordinates in the two mentioned systems (*M. Lagally*, 1934 (241)), we write the radius vector  $\underline{r}$  in the double form

$$\underline{r} = x\underline{i} + y\underline{j} + z\underline{k} = x'\underline{i}' + y'\underline{j}' + z'\underline{k}'. \quad (55)$$

By scalar multiplication of these equations one after the other by  $\underline{i}$ ,  $\underline{j}$ ,  $\underline{k}$ , and  $\underline{i}'$ ,  $\underline{j}'$ ,  $\underline{k}'$ , respectively, we obtain the formulas of the coordinates  $x$ ,  $y$ ,  $z$ , and  $x'$ ,  $y'$ ,  $z'$ , respectively. We need the first mentioned coordinates, only, which thus become

$$\begin{aligned}
x &= (\underline{r} \underline{i}) = (\underline{i} \underline{i}') x' + (\underline{i} \underline{j}') y' + (\underline{i} \underline{k}') z' \\
&= \cos(x, x') x' + \cos(x, y') y' + \cos(x, z') z' \\
y &= (\underline{r} \underline{j}) = (\underline{j} \underline{i}') x' + (\underline{j} \underline{j}') y' + (\underline{j} \underline{k}') z' \\
&= \cos(y, x') x' + \cos(y, y') y' + \cos(y, z') z' \\
z &= (\underline{r} \underline{k}) = (\underline{k} \underline{i}') x' + (\underline{k} \underline{j}') y' + (\underline{k} \underline{k}') z' \\
&= \cos(z, x') x' + \cos(z, y') y' + \cos(z, z') z'.
\end{aligned} \tag{56}$$

If we denote a displacement (due to Brownian movements) in the direction of the  $X$ -axis as  $\Delta x$ , in the  $X'$ -axis as  $\Delta x'$ , and so on, we get

$$\Delta x = \cos(x, x') \Delta x' + \cos(x, y') \Delta y' + \cos(x, z') \Delta z' \tag{57}$$

and analogous expressions for  $\Delta y$  and  $\Delta z$ .

We calculate then for a fixed position  $x', y', z'$  of the ellipsoid the mean squares of the displacements, hence

$$\begin{aligned}
\overline{\Delta x^2} \Big|_{x', y', z' \text{ fixed}} &= \cos^2(x, x') \overline{\Delta x'^2} \Big|_{x', y', z'} + \cos^2(x, y') \overline{\Delta y'^2} \Big|_{x', y', z'} \\
&+ \cos^2(x, z') \overline{\Delta z'^2} \Big|_{x', y', z'} + 2 \cos(x, x') \cos(x, y') \overline{\Delta x' \Delta y'} \Big|_{x', y', z'} \\
&+ \dots \dots \dots \tag{58}
\end{aligned}$$

and analogous

$$\overline{\Delta y^2} \Big|_{x', y', z' \text{ fixed}} \quad \text{and} \quad \overline{\Delta z^2} \Big|_{x', y', z' \text{ fixed}}. \tag{59}$$

By a generalization of *Einstein's* well-known formula (for the displacement of a sphere along the  $X$ -axis)

$$\overline{\Delta x^2} = \frac{R \Theta}{N} \frac{1}{3 \pi \eta r} \Delta t = 2 \frac{k \Theta}{f} \Delta t \tag{60}$$

( $f = 6 \pi \eta r$  is the resistance coefficient of the translation of the sphere), we get for the displacement in the direction of the principal axes of the ellipsoid

$$\overline{\Delta x'^2} = 2 \frac{k \Theta}{f_1} \Delta t = 2 D_1 \Delta t, \tag{61}$$

where  $f_1$  is the resistance coefficient for the movement in the direction of the  $X$ -axis, and  $D_1$  is the corresponding diffusion coefficient.

Analogous expressions are valid for

$$\overline{\Delta y'^2} \quad \text{and} \quad \overline{\Delta z'^2}, \quad (62)$$

when  $\Delta t$  is chosen in such a way that the rotation of the ellipsoid is small.

In the classical way, the mean of the products is equal zero,

$$\overline{\Delta x' \Delta y'} = 0 \text{ etc.} \quad (63)$$

By substitution of the expressions found in the above equation, we get

$$\overline{\Delta x^2} \Big|_{x', y', z' \text{ fixed}} = 2k \Theta \left\{ \frac{\cos^2(x, x')}{f_1} + \frac{\cos^2(x, y')}{f_2} + \frac{\cos^2(x, z')}{f_3} \right\} \Delta t \quad (64)$$

and analogous

$$\overline{\Delta y^2} \Big|_{x', y', z' \text{ fixed}} \quad \text{and} \quad \overline{\Delta z^2} \Big|_{x', y', z' \text{ fixed}} \quad (65)$$

If we now assume  $f_2 = f_1$  (ellipsoid of revolution), we obtain

$$\overline{\Delta x^2} \Big|_{x', y', z' \text{ fixed}} = 2k \Theta \Delta t \left\{ \frac{[\cos^2(x, x') + \cos^2(x, y')]}{f_1} + \frac{\cos^2(x, z')}{f_3} \right\}. \quad (66)$$

We now find the mean value of this magnitude over all possible positions of the system of principal axes  $X'$ ,  $Y'$ ,  $Z'$ , on the simplified assumptions that the time of observation  $\Delta t$  is suitably small, so that the rotations within this space of time are very small.

$\cos(x, x')$ ,  $\cos(x, y')$ ,  $\cos(x, z')$  are the direction cosines of the unit vector  $\underline{i}$  relative to the labelled system, hence  $\cos(x, x')$ ,  $\cos(x, y')$  are components of the projection of  $\underline{i}$  on the  $X'$ ,  $Y'$ -plane. In other words,

$$\cos^2(x, x') + \cos^2(x, y') = \cos^2 \chi \quad (67)$$

is the square of the length of the projection of  $\underline{i}$  on the  $X'$ ,  $Y'$ -plane, or the square of the cosine to the angle between the  $X'$ ,  $Y'$ -plane and the  $X$ -axis. This magnitude ( $\cos^2 \chi$ ) is unchanged when the labelled mobile system is turned around a fixed  $Z'$ -axis in a given direction. In the same way,  $\cos(x, z')$  is constant at such a rotation.

Since all positions to which the  $X'$ -axis might adjust itself during rotation are equally probable, we get as the mean value from all positions which correspond to a given direction of the symmetry axis, *i. e.* the  $Z'$ -axis,

$$\overline{\Delta x^2} \Big|_{z' \text{ fixed}} = 2 k \Theta \Delta t \left\{ \frac{\cos^2 \chi}{f_1} + \frac{\cos^2(x, z')}{f_3} \right\}, \quad (68)$$

where  $\chi$  is the angle between the  $X$ -axis and a plane vertical to the  $Z'$ -axis. Since we only have to reckon with  $\cos^2 \chi$ , it is the same whether  $\chi$  is the obtuse or the acute angle.

If we introduce — in order to characterize the  $Z'$ -axis, *i. e.* the direction of the symmetry axis — a polar coordinate system  $(\theta, \phi)$  with the  $X$ -axis as polar axis,  $\theta =$  the angle  $(x, z')$ , and  $\phi =$  the angle between the  $Y$ -axis and the projection of the  $Z'$ -axis on the  $Y, Z$ -plane, we may write

$$\chi = \theta - \frac{\pi}{2} \quad \text{or} \quad \chi = \theta + \frac{\pi}{2} \quad i. e. \quad (69)$$

$$\cos^2 \chi = \sin^2 \theta \quad \text{and} \quad \cos^2(x, z') = \cos^2 \theta.$$

Since the probability for the different directions of the  $Z'$ -axis is the same in all directions, so that the probability to find the direction within the solid angle element  $d\Omega = \sin \theta d\theta d\phi$  is proportional to  $d\Omega$ , the required mean value over all ellipsoids is given by

$$\overline{\Delta x^2} = 2 k \Theta \Delta t \left\{ \frac{\frac{1}{4\pi} \int \cos^2 \chi d\Omega}{f_1} + \frac{\frac{1}{4\pi} \int \cos^2 \theta d\Omega}{f_3} \right\},$$

$$\frac{1}{4\pi} \int \cos^2 \chi d\Omega = \frac{1}{4\pi} \int_0^\pi \sin^2 \theta \sin \theta d\theta \int_0^{2\pi} d\phi = \frac{1}{2} \left\{ - \int_1^{-1} (1-x^2) dx \right\} = \frac{2}{3},$$

$$\frac{1}{4\pi} \int \cos^2 \theta \sin \theta d\theta \int_0^{2\pi} d\phi = - \frac{1}{2} \int_1^{-1} x^2 dx = \frac{1}{3}, \quad (70)$$

hence

$$\overline{\Delta x^2} = 2 k \Theta \frac{1}{3} \left\{ \frac{2}{f_1} + \frac{1}{f_3} \right\} \Delta t = 2 \frac{2D_1 + D_3}{3} \Delta t = 2 D_m \Delta t.$$

The mean diffusion coefficient  $D_m$  of an ellipsoid of revolution is the arithmetic mean of the coefficients for the diffusion in the



direction of the principal axes; the same consideration applies to the mean resistance coefficient.

If  $f_1 = f_2 = f_3$  or  $D_1 = D_2 = D_3$ , the formula found becomes identical with *Einstein's* formula.

The calculation of the mean squares of the displacements, taking into account the rotation of the ellipsoid, was carried out by *F. Perrin*, 1936 (329). However, his final result is wrong due to a number of errors in the calculation.

Finally, some numerical calculations concerning a given ellipsoid by means of the formulas described in § 22, p. 54, should be mentioned.

In the case of an oblate ellipsoid of revolution with the semi-axes  $a = 1.2 \cdot 10^{-4}$  cm and  $b = c = 4 \cdot 10^{-4}$  cm which is freely movable in a medium with the internal friction  $\eta = 0.019$  Poise and the absolute temperature  $\Theta = 293^\circ$  Kelvin (*Boltzmann's* constant  $k = 1.371$  erg/ $^\circ$ C), we get a mobility

$$\frac{1}{f_a} = 7.99 \cdot 10^3, \quad \frac{1}{f_b} = \frac{1}{f_c} = 9.90 \cdot 10^3 \quad \text{and} \\ \frac{1}{F} = \frac{1}{3} \left( \frac{1}{f_a} + \frac{2}{f_b} \right) = 9.26 \cdot 10^3 \text{ gram}^{-1} \text{ cm}^{-1} \text{ sec}^2,$$

and hence the diffusion coefficients

$$D_a = 3.21 \cdot 10^{-10}, \quad D_b = D_c = 3.98 \cdot 10^{-10}, \\ D_m = 3.72 \cdot 10^{-10} \text{ cm}^2 \text{ sec}^{-1}.$$

The rotation mobilities become

$$\frac{1}{R_a} = 5.53 \cdot 10^{10}, \quad \frac{1}{R_b} = 8.65 \cdot 10^{10}.$$

By means of

$$\frac{1}{6 \pi \eta r_{\text{equiv}}} = \frac{1}{F}$$

we get

$$r_{\text{equiv}} = 3.16 \cdot 10^{-4} \text{ cm}.$$

For the mean translation in the direction of the *X*-axis after 30 sec. it was found

$$\bar{X}_a = 1.39 \cdot 10^{-4} \text{ cm}, \quad \bar{X}_{b,c} = 1.55 \cdot 10^{-4} \text{ cm},$$

and for a sphere with a radius which is equal to the found equivalent radius of the ellipsoid

$$\overline{X}_{equiv} = 1.49 \cdot 10^{-4} \text{ cm.}$$

The mean rotation displacements around the  $a$ - and  $b(c)$ -axes after 30 sec is

$$\Delta r_a = 21^\circ \quad \Delta r_b = 26^\circ.$$

## § 36. THEORETICAL INVESTIGATIONS CONCERNING THE CONDUCTIVITY PHENOMENON.

With respect to a later application of conductometry to the experimental investigation of erythrocyte aggregations and, furthermore, in consideration of the significance of some conductivity phenomena (*cf.* p. 93) for the electric conductivity of the blood in general, an attempt will be made to answer the following questions.

- I. How does a suspension conduct the electric current?
- II. Which possibilities exist for the appearance of a time-dependent change of the conductivity?

The conductivity of a suspension is due

- A. partly to the direct conduction through the suspension medium and the particles, depending
  - 1) on the specific conductivities of the suspension medium and the particles,
  - 2) on the volume concentration of the particles and, furthermore, for suspensions of non-spherical particles,
  - 3) on shape and orientation of the particles;
- B. partly to the cataphoretic conduction caused by the particles.

*Direct electric conduction. (Ad A.).*

*Ad A 1).*

*Can electrolyte shifts between the suspension medium and the corpuscles, accompanying aggregation, produce the conductivity phenomenon?*

An alteration of the specific conductivity of the dispersion medium may be caused by a changed electrolyte content, either

due to adsorption of electrolyte to the aggregating particles or due to a change in electrolyte distribution between the suspension medium and the internal phase of the corpuscles, or due to both these phenomena.

In the case of blood corpuscles, a variation of the specific conductivity of the particles may be caused by changes of the surface permeability, but hardly by a small change of the electrolyte content; considering an electrolyte shift, it seems therefore reasonable to assume only a change in the specific conductivity of the dispersion medium, while that in the blood corpuscles is regarded as constant.

*H. Fricke*, 1924 (131), found a formula for the direct conductivity of a suspension of homogeneous spheroids, *viz.*

$$\frac{k - k_1}{k - k_2} \left( 1 - \frac{k_2}{k_1} \right) = \beta \frac{\rho}{1 - \rho}, \quad (71)$$

where  $k$  is the specific conductivity of the suspension,  $k_1$  that of the suspension medium, and  $k_2$  that of the particles.  $\beta$  depends in a very complicated way upon the lengths of the axes of the spheroids ( $a$  and  $b$ ) and on the ratio  $\frac{k_2}{k_1}$ ;  $\rho$  is the volume concentration of the particles, *i. e.* that fraction of a volume unit of the suspension which is occupied by the disperse phase.

If  $\frac{a}{b} \approx \frac{1}{4}$ ,  $k_2 = 0^*$ ), we get  $\beta = -1.91$  so that the formula in this case becomes

$$1 - \frac{k_1}{k} = 1.91 \frac{\rho}{1 - \rho}. \quad (72)$$

At a constant volume concentration, a decrease in  $k_1$ , *e. g.* by reduction of the electrolyte content, involves a decrease in  $k$ . A lowering of the electrolyte content of the plasma (or the serum), however, will produce a still further reduction of  $k$ , since the increasing volume concentration of the erythrocytes due to a lower osmotic pressure in the outer phase also causes a decrease in  $k$ .

Numerous authors have studied the influence of the volume concentration  $\rho$  on the conductivity of corpuscle suspensions with

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\*) Conventionally, the blood corpuscles are considered to be insulators since their conductivity makes out less than 1 per cent of that of the plasma. *S. C. Brook's* deviating view-point, 1925 (48), was disproved by *G. W. Stewart*, 1929 (398).

the aim to determine the erythrocyte volume. (W. Roth, 1897/98 (357), S. Bugarszky and F. Tangl, 1897/98 (50), G. N. Stewart, 1899 (397) and 1929 (398), P. Fraenkel, 1904 (120), R. Ege, 1920 (90), and H. C. Gram, 1924 (158)). Moreover, the change in the erythrocyte volume at different osmotic pressures of the substances in the suspension medium was elucidated (R. Ege, 1919 (89), and E. Schiødt, 1931 (368)). According to R. Ege, the change in volume follows *Boyle-Mariotte's law*

$$P_0(V_0 - x) = P_1(V_1 - x), \quad (73)$$

where  $V_0$  and  $V_1$  are the volumina of the blood corpuscles in two different media with the osmotic pressure  $P_0$  and  $P_1$ ;  $x$  is the magnitude of the disperse phase of the corpuscles (within the corpuscles) which is supposed not to participate in the swelling up or crumbling of the erythrocytes.  $x$  is generally put equal to 50 per cent; cf. E. Schiødt's calculations, 1931 (368), which are based upon I. Christensen and E. J. Warburg's measurements of the depression of the freezing point (66).

Finally, we have the complicated electrolyte equilibria (*Donnan equilibrium*) between suspension fluid and erythrocytes. A change in the electric conductivity of a corpuscle suspension due to a change in the electrolyte content of the suspension medium may therefore primarily be determined by direct measurements.

By the usual analytical methods, a determination of minute electrolyte shifts is very difficult to perform; indirect methods, however, such as conductivity- and possibly also potentiometric measurements (e. g.  $p_H$  measurements of the blood and the plasma belonging to it after the corpuscles have been centrifuged off) seem to be valuable for this purpose.

Judging from the above cited literature (p. 92), a "suspension effect" of corpuscle-plasma suspensions hardly exists; the fact that rouleaux show the same electrokinetic potential as single blood corpuscles also is against such an effect (cf. p. 38).

Ad A 2).

*Does a change in the size of the particles due to occurring agglomeration cause the conductivity effect?*

When considering a suspension of homogeneous, equally large spheres, where several spheres associate to larger ones so that

the volume of the disperse phase (volume concentration) remains unchanged, we find constant conductivity. Furthermore, *Fricke's* formula shows that the conductivity must be independent of the size of the particles since the characteristic magnitudes of *Fricke's* calculations (130), viz. the electric field intensity normal to the outer surface of a particle (sphere) and the field intensity normal to the internal surface, are independent of the radius. *M. Oker-Blom*, 1900 (310), performed some classical measurements on suspensions with unequally large quartz particles and he, too, found that the conductivity was independent of the size of the particles.

*Is the change in conductivity caused by a change in the volume concentration of the particles?*

*S. C. Brooks*, 1925 (48), pointed at the influence of small changes in volume of the blood corpuscles on the electric conducting properties of the blood. *Brooks'* special view assuming a higher conductivity of the red blood corpuscles is in contrast to *W. Roth* (357), *S. Bugarszky* and *F. Tangl* (50), *G. W. Stewart* (397), *M. Oker-Blom* (309), and *H. Fricke* (130) who considered the erythrocytes to be insulators\*).

In "rouleaux formations", a pressing together of the erythrocytes may be observed directly (*R. Fåhræus* (109), *E. Ponder* (336)); in this way, only a deformation might occur, while a volume reduction is hardly probable. In regular rouleaux formations, and especially in very large erythrocyte aggregates where we presumably meet with spongy structures, larger or smaller amounts of plasma might be enclosed. Hence, in this case, the aggregation should cause an apparent increase in volume concentration of the corpuscles, i. e. a reduction of the conductivity. By means of *Fricke's* formula cited above, a change in volume concentration corresponding to a given change in conductivity can be calculated. Obviously, a given increase in corpuscle concentration causes the greater a decrease in conductivity of the blood, the greater the initial concentration of the corpuscles.

Ad A 3).

*Can a different shape of the particles cause a change in conductivity?*

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\*) Cf. footnote p. 116.

As shown by *H. Fricke*, 1924 (132, p. 581), the conductivity of a suspension also depends on the shape of the particles. The observation of a pressing together of the erythrocytes during rouleaux formation has been discussed previously. *J. F. McClendon*, 1926 (274), discussed the problem whether a change in the shape of erythrocytes from ellipsoid to sphere might produce a lowering of the conductivity. A change in shape in the opposite direction, originating from an influence of the electrical charges of the double layer on the interfacial tension, was assumed by *Y. Björnståhl*, 1924 (37), in order to explain the "electric double refraction" of mercury suspensions.

*E. Muth*, 1927 (285), observed the so-called "string of pearls" phenomenon, *i. e.* drops of fat, emulgated in water, arranging themselves like pearls on a string (presumably a simultaneous length deformation of the fat drops occurred) parallel to the direction of the field when an alternating field was applied. This phenomenon is certainly bound to strong alternating fields. *E. Muth's* experiment was carried out with dilute milk, the particles were  $0.5\text{--}5\ \mu$ . The frequency of the a. c. varied from  $2 \cdot 10^4$  to  $2 \cdot 10^6$  cycles. On three emulsions investigated, the effect was independent of frequency within the given range. Presumably, the time of relaxation of the ionic atmosphere of a particle is considerably greater than the time of relaxation of the atmosphere of an ordinary electrolyte ion, so that low frequencies should be of considerable interest.

The lowest field intensities (threshold values) just producing the "string of pearls" phenomenon were 3, 4, and 10 volts/cm. The mentioned field intensity as well as the frequency are much higher than those employed in the author's conductometric measurements (2000 cycles, 0.02 volt/cm; *cf.* p. 181).

In "string of pearls" formations, the electric conductivity of emulsions (or suspensions) presumably increases (the particles are regarded as insulators). A mathematical treatment of *Muth's* phenomenon was attempted by *W. Krasny-Ergen*, 1936 (232), who calculated the behaviour of two insulated conducting spheres. During direct observation of erythrocytes in the electric field, for example in the usual micro cataphoresis apparatus (direct current), a change in shape of the erythrocytes simultaneously with the switching on of the field could not be noticed.

Does the so-called "orientation effect" play any part in the change of conductivity?

This question is answered in § 37 (p. 125) which contains the author's theoretico-physical investigations concerning this effect.

*The cataphoretic conduction. (Ad B).*

The electric conductivity of an arbitrary medium is determined partly by the quantity of electricity moved in the electric field, partly by the velocity with which the carriers of the electric charge move in the given field. In the conduction through an electrolyte solution, the ions appear as carriers of electricity. In suspensions, the cataphoretic migration of the particles causes an electric conduction, the so-called cataphoretic conduction, and thereby the conductivity of the suspension is increased (*M. v. Smoluchowski*, 1903 (381) and 1905 (382)).

Colloidal particles do not carry any free electric charges but, according to *Helmholtz-Smoluchowski's* theory, 1879 (185) and 1912/21 (385), they are surrounded by an electric double layer (*cf.* § 23, p. 57). When an electric field is applied, the double layer is displaced, the particles move and transport a quantity of electricity, the inversely charged layer of fluid moving analogously. The corresponding contribution to the conductivity of the system is determined by the effective charges of the particles, their number, their friction resistance, and by the charges of the migrating layers of the fluid.

It appears from *H. Freundlich's* and *G. Hevesy's* calculations, 1932 (125, II, p. 63) and 1917 (197), respectively, that due regard must be paid to the cataphoretic conductivity when measuring the conductivity of aqueous suspensions. For a suspension of spherical particles, the cataphoretic conductivity (*Freundlich* and *Hevesy*, *loc. cit.*) is

$$\lambda_{\omega} = \nu \frac{4 \pi \eta u r (r + d)}{N d} u \quad (74)$$

(number of particles times valency times migration velocity), where  $\lambda_{\omega}$  is the specific conductivity,  $\nu$  the number of particles per cc,  $\eta$  the coefficient of internal friction of the suspension medium,  $r$  the radius of the particles,  $u$  the cataphoretic migrat-

ion velocity of the particles at a fall of potential of 1 volt per cm,  $d$  the thickness of the double layer, and  $N$  the *Avogadro-Loschmidt* number. If also the participation of the outer shell of the double layer in the transport of electricity is taken into account, the expression has to be multiplied by the factor 2. In case of hydrogen ions as "counter ions", this factor may increase to 8. It appears from the formula that the cataphoretic conductivity is directly proportional to the number of particles; furthermore, the size of the particles plays an essential part, since the conductivity increases approximately with the square of the radius. In spite of the low concentration of particles in the blood compared with ordinary hydrophobic colloids showing a just measurable cataphoretic conductivity, we must expect a marked cataphoretic conductivity of the blood due to the enormous size of the corpuscles relative to the size of ordinary colloidal particles (*cf.* the calculation below).

The cataphoretic conductivity of a suspension is generally constant and is part of the total conductivity of the suspension, where it will only be noticed if it is changed. Since the cataphoretic conductivity of a suspension is proportional to the number of particles and to the square of their radius, *i. e.* the size of the interface between the particles and the suspension medium, a coagulation process should be accompanied by a reduced cataphoretic conduction (if the thickness of the double layer and the cataphoretic migration velocity are considered constant).

*H. Nordenson*, 1915 (296), and furthermore *G. Hevesy*, 1917 (197), assumed that the electric conductivity of a dispersoid may decrease due to an increase in size of the particles. As an example, *Hevesy* mentioned *Whitney* and *Blake's* results from conductivity measurements on colloidal gold solutions (1904 (444)). The conductivity decreased after repeated cataphoretic deposition and solution of the gold. The decrease in conductivity might be caused either by removal of the electrolytes or by continuous increase in size of the gold particles after repeated dissolving.

The reduced conductivity as a function of a decreasing degree of dispersion is illustrated in the following table calculated by *Hevesy*. This table shows the conductivity of a 0.1 per cent gold hydrosol with a "normal" cataphoretic mobility of the particles



(50 ohms<sup>-1</sup> cm<sup>2</sup>, or  $5.2 \cdot 10^{-4}$  cm<sup>2</sup> · sec<sup>-1</sup> volt<sup>-1</sup>) and a thickness of the double layer of  $5 \cdot 10^{-7}$  cm.

Table 3.

The cataphoretic conductivity of suspensions.  
(According to G. Hevesy, 1917 (197)).

Radius of particles in cm	Number of particles per cc	Valency of the aggregates	Specific conductivity in ohm <sup>-1</sup> cm <sup>-1</sup>
$10^{-7}$	$1.2 \cdot 10^{16}$	5	$0.5 \cdot 10^{-6}$
$10^{-6}$	$1.2 \cdot 10^{13}$	120	$1.2 \cdot 10^{-7}$
$10^{-5}$	$1.2 \cdot 10^{10}$	8350	$8.4 \cdot 10^{-9}$

H. Freundlich, 1932 (125, II, p. 64), calculated a similar series of figures, where the conductivity was moreover evaluated for different thicknesses of the *Helmholtz'* double layer; the cataphoretic conductivity increases with increasing thickness of the double layer. The increased contribution of the single particle to the conductivity due to increasing radius will be over-compensated by the decrease in the number of particles. If the number of particles is reduced  $k$  times (to  $\frac{1}{k}$ ) by the formation of exclusively  $k$ -fold aggregates, the radius of the aggregates becomes  $r \sqrt[3]{k}$ , and the surface of the particles which is proportional to the conductivity contribution of the single aggregate becomes  $\pi r^2 k^{2/3}$ . These absolute calculations of the cataphoretic conductivity — on the basis of Hevesy's, Nordenson's, and others' formulas — are only of minor significance, since our knowledge of the structure of colloidal solutions is very insufficient.

The experimental determination of the cataphoretic conductivity of a colloid is not solved satisfactorily. In general, a difference method is employed in which either the directly measured or the calculated conductivity of the ions which do not belong to the considered colloidal salt (*i. e.* the particles with "counterions") is subtracted from the measured conductivity of the suspension. In some of the first experiments with the difference-method, ultrafiltration has been applied. J. Duclaux, 1909 (86), thus described the cataphoretic conductivity of the colloid by the formula

$$\lambda_x = \lambda - \lambda_u (1 - v), \quad (75)$$

where  $\lambda_x$  is the conductivity of the suspension,  $\lambda_u$  that of the ultrafiltrate, and  $v$  is the volume concentration of the particles. *Duclaux*' equation cannot be applied directly to corpuscle suspensions, since the volume concentration of red cells plays a rôle even in rather dilute suspensions, in contrast to ordinary colloidal particles in concentrated sols. The volume concentration is of great influence on the direct conduction of suspensions. The experimentally found cataphoretic conductivity is generally not identical with the theoretically calculated conductivity but it is a few orders of magnitude higher. Furthermore, we meet with the peculiar phenomenon that the conductivity of the ultrafiltrate can be greater than that of the suspension. The application of ultrafiltration is an intervention which in itself might cause critical objections when colloid electrolytes are concerned (*cf.* *Wiegner*'s suspension effect discussed on p. 92); in most cases, the results become falsified.

The colloid-chemical handbook by *W. Pauli* and *E. Valkó*, 1929 (325), presents an excellent survey of the lacking agreement between the experimentally found and the calculated conductivity of colloids\*).

*A rough estimate of the cataphoretic conductivity of the blood.*

*H. Freundlich*, 1932 (125, II, p. 87), has given a simple formula for the calculation of the electric charge of a colloidal particle if the cataphoretic conductivity of the colloid is known, or *vice versa*. The cataphoretic conductivity  $\lambda_\omega$  of a suspension indicates that the particles carry  $\lambda_\omega$  coulombs across every  $\text{cm}^2$  per sec, when the intensity of the field is 1 volt per cm. When the cataphoretic velocity of the particles in the mentioned field amounts to  $u$  cm/sec, this means that a sol-volume of  $u$  cc, containing  $uv$  particles, passes  $1 \text{ cm}^2$  per sec so that the charge per single particle becomes

$$e = \frac{\lambda_\omega}{v u} \text{ coulombs} = 6 \cdot 10^{18} \cdot \frac{\lambda_\omega}{v u} \text{ electronic charges.}$$

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\*) *Addendum*: A charge of 30 units was calculated from the cataphoretic velocity of particles in a gold sol, while a charge of 40,000 units was obtained in conductivity measurements (*loc. cit.* (325 p. 497)).

On the other hand, we have

$$\lambda_{\omega} = \frac{e v u}{6 \cdot 10^{18}}. \quad (76)$$

This formula does not contain any hypothetic thickness of the double layer. The charge of the particles calculated by means of the formula, *viz.* the cataphoretic conductivity, must be regarded as a maximum value. If the contribution from the "counter ions" is also taken into account, the cataphoretic conductivity amounts to more than twice to three times  $\lambda_{\omega}$ .

The number of blood corpuscles bc	$\nu = 5 \cdot 10^9/\text{cc}$
the cataphoretic velocity	$u = 1 \cdot 10^{-4} \text{ cm/sec./}$ volt/cm
the charge number	$e = 15 \cdot 10^6 \text{ electronic}$ charges

(according to *H. Abramson* and *L. S. Moyer*, *cf.* above, p. 62)  
we get

$$2\lambda_{\omega} = c \cdot 2 \cdot 10^{-6} \text{ ohm}^{-1} \text{ cm}^{-1}$$

and, hence, the conductivity makes out 0.4‰ of the conductivity of ordinary blood, *viz.*  $5 \cdot 10^{-3} \text{ ohm}^{-1} \text{ cm}^{-1}$ .

If we assume, however, a charge of the erythrocytes which is 50 times as high, *i. e.*  $e = 75 \cdot 10^7$  electronic charges, which is not at all improbable, we get  $2\lambda_{\omega} = 1 \cdot 10^{-4} \text{ ohm}^{-1} \text{ cm}^{-1}$ , or 2 per cent of the conductivity of the suspension.

When the cataphoretic conductivity of the blood is of a reasonable order of magnitude, we should expect that the conductivity of the blood calculated according to *Fricke's* formula — who only reckons with direct conduction — should be less than the experimentally determined conductivity. *H. Fricke*, 1924 (131), found rather good agreement of his calculations with *G. N. Stewart's* measurements, 1899 (397). However, both the experimental errors and especially the actually unknown conductivity of the erythrocytes make a decision on the basis of this method impossible.

# § 37. THEORETICO-PHYSICAL INVESTIGATION OF THE SO-CALLED "ORIENTATION EFFECT"\*)

## Introduction.

*H. Fricke*, (132, p. 581, and 134, p. 159), *J. F. McClendon* (274), and others presumed that an orientation of the erythrocytes in the electric field might cause a change in the electric conductivity of the blood. Incited by this interesting presumption and, furthermore, bearing in mind the general significance of this problem for colloid physics, the author is discussing in the following paragraph how the direct conduction of a suspension can be changed when non-spherical particles orientate themselves in the suspension medium.

The liquid suspension medium is assumed to have a dielectric constant  $\epsilon_0$  and an electric conductivity  $\sigma_0$ ; the suspended, unelastic ("starr elastische") particles, which are assumed to be ellipsoids of revolution, may have the corresponding constants  $\epsilon$  and  $\sigma$ . Provided that the conductivity of the ellipsoids is different from that of the suspension medium, the conductivity of the suspension will depend upon the orientation of the particles and will reach an extreme value (maximum) if all ellipsoids are adjusted with their major axes parallel to the direction of the current, and the other extreme value (minimum) if the ellipsoids are orientated completely at random. When  $\epsilon_0 \neq \epsilon$  or  $\sigma_0 \neq \sigma$ , or both, ponderomotive forces will act upon the ellipsoids which thereby get a moment of rotation and tend to obtain a certain orientation.

We therefore meet with the task to follow more closely this orientation process when an electric field is applied and to study the resulting changes in conductivity. We consider the electric rotation moment, the opposing moment of friction arising from the rotation of the ellipsoids, and the influence of the Brownian movements upon an incipient orientation. The conductivity of the suspension may then be calculated at a given orientation of the ellipsoids.

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\*) The results from investigations described in this paragraph have been published recently (*J. E. Thygesen*, 1939 (414)).

a. *The electric rotation moment.*

The electrodes of the conductivity cell be two vertical plates whose distance is small compared with their dimensions.

When no ellipsoids are present between the electrodes, the field is homogeneous with horizontal lines of force. When an ellipsoid is placed between the electrodes, the field will be deformed locally and the ellipsoid will be affected by a rotation momentum  $D$ .

The origin of a rectangular right-coordinate system is placed in the centre of the ellipsoid so that its  $x$ -axis overlaps the axis of symmetry (the short semi-axis of planetary (oblate) ellipsoids of revolution, the long semi-axis of prolate ellipsoids). Since we consider an ellipsoid of revolution, the  $z$ -axis may be chosen normal to the plane formed by the  $x$ -axis and the outer given field vector, field intensity  $E$ , so that  $E_z = 0$ . The  $y$ -axis is then determined. The acute angle between the axis of symmetry ( $x$ -axis) and the field vector is denoted as  $\theta$ .

The moment of revolution exerted upon the ellipsoid by the given field was calculated by *R. Fürth*, 1924 (140) and 1927 (142). Retaining his terms we get

$$D = \frac{2 \epsilon_0 E^2 \sin 2\theta}{\left(X_0 + \frac{4}{\mu - 1}\right) \left(Y_0 + \frac{4}{\mu - 1}\right)} \frac{b^2}{a^2} (a^2 - b^2) \lambda, \quad (77)$$

where

$$\lambda = \int_{-a}^{+a} \frac{x^2 (a^2 - x^2)}{x^2 \left(1 - \frac{b^2}{a^2}\right) - a^2} dx, \quad \mu = \frac{\sigma}{\sigma_0},$$

and  $X_0$  and  $Y_0$  are constants. The moment of revolution is positive and tends to increase  $\theta$  when  $a < b$ , and it is negative, tending to decrease  $\theta$ , when  $a > b$ .

For oblate ellipsoids of revolution, we have

$$\begin{aligned} \frac{b}{a} &= \kappa > 1; \lambda = \frac{-2a^3}{(\kappa^2 - 1)^2} \left( \frac{1}{3} - 2\sqrt{\kappa^2 - 1} \arctan \sqrt{\kappa^2 - 1} + \frac{2}{3} \kappa^2 \right) \\ X_0 &= \frac{4\kappa^2}{\kappa^2 - 1} \left[ 1 - \frac{\pi}{2\sqrt{\kappa^2 - 1}} + \frac{1}{\sqrt{\kappa^2 - 1}} \arctan \frac{1}{\sqrt{\kappa^2 - 1}} \right] \\ Y_0 &= \frac{2\kappa^2}{\kappa^2 - 1} \left[ -\frac{1}{\kappa^2} + \frac{\pi}{2\sqrt{\kappa^2 - 1}} - \frac{1}{\sqrt{\kappa^2 - 1}} \arctan \frac{1}{\sqrt{\kappa^2 - 1}} \right]. \end{aligned} \quad (78)$$

For prolate ellipsoids of revolution

$$\begin{aligned}\frac{b}{a} &= \kappa < 1; \lambda = \frac{-2a^3}{(1-\kappa^2)^2} \left( \frac{1}{3} + \frac{2\kappa^2}{3} + \frac{\kappa^2}{2\sqrt{1-\kappa^2}} \log \frac{1-\sqrt{1-\kappa^2}}{1+\sqrt{1-\kappa^2}} \right) \\ X_0 &= \frac{4\kappa^2}{1-\kappa^2} \left[ -1 + \frac{1}{2\sqrt{1-\kappa^2}} \log \frac{1+\sqrt{1-\kappa^2}}{1-\sqrt{1-\kappa^2}} \right] \\ Y_0 &= \frac{\kappa^2}{1-\kappa^2} \left[ \frac{2}{\kappa^2} - \frac{1}{\sqrt{1-\kappa^2}} \log \frac{1+\sqrt{1-\kappa^2}}{1-\sqrt{1-\kappa^2}} \right].\end{aligned}\quad (79)$$

These equations indicate that the expression for  $D$  is independent of the ellipsoidal dielectric constant  $\epsilon$ , owing to the fact that the electric field inside the ellipsoid is homogeneous. The moment of revolution is proportional to the square of the field intensity so that  $D$  is independent of the direction of the field.

As stated by *Fürth*, the expression for  $D$  applies to quasistationary states only (*cf.* his discussion with *Busch*, 1924 (141)).

As the moment of revolution results essentially from an accumulation of electricity on the surface of the ellipsoid due to the difference in conductivity of the ellipsoid and the suspension medium, we have  $D = 0$  for  $\sigma_0 = \sigma$ .

Since  $D$  is proportional to  $\sin 2\theta$ , the moment of revolution will be a maximum if  $2\theta = \frac{\pi}{2}$  or  $\theta = 45^\circ$ . If  $0 < \theta < \frac{\pi}{2}$ ,  $D$  has a definite sign, positive for oblate, and negative for prolate ellipsoids.  $D = 0$  if the axis of symmetry is parallel to the direction of the lines of force or normal to them.

$X_0$ ,  $Y_0$ ,  $a$ ,  $b$ , and  $\lambda$  depend only on the geometrical shape of the ellipsoid; if  $a = b$ , we have  $D = 0$ .  $X_0 = 2ab^2A$ , and  $Y_0 = 2ab^2B$ , where  $A$  and  $B$  are the elliptic integrals mentioned on page 56.

Hence, independent of the magnitude of its electric constants ( $\epsilon \gtrless \epsilon_0$ ,  $\sigma \gtrless \sigma_0$ ), the ellipsoid will tend to adjust its major axis parallel to the field.

In the present calculations, the cataphoresis phenomenon is not taken into account. The increase in conductivity of the suspension (*cf.* p. 121) is constant, and the cataphoretic motion is without any influence on the orientation effect since the sym-

metrical distribution of charges in the double layer cannot produce any rotation of the ellipsoids.

An orientation of the particles in the direction of least hydrodynamic resistance caused by cataphoresis, electro-endosmotic flow, or translational Brownian movements does not occur, as we cannot speak of a minimal principle of liquid resistance (*R. Gans*, 1911 (144), and *C. E. Marshall*, 1930 (272)). In narrow vessels, however, the different velocities of the liquid layers may cause some orientation (*cf.* orientation of particles by "streaming double refraction").

The cataphoretic migration velocity is small\*) and, according to *Helmholtz-Smoluchowski's* theory, 1912/21 (385), and *H. Freundlich* and *H. A. Abramson's* experiments, 1928 (127) (*cf.* pp. 39 and 60), it is independent of the shape of the particles, *i. e.* of the orientation of the ellipsoids.

#### *b. The hydrodynamic problem.*

As already mentioned on p. 57, the required resistance coefficient  $\xi$  for the rotation of an ellipsoid of revolution about an axis normal to the axis of symmetry is

$$\xi = \frac{16\pi\eta}{3} \frac{a^2 + b^2}{a^2A + b^2B}, \quad (80)$$

where  $a$  and  $b$  are the lengths of the semi-axes,  $\eta$  the coefficient of internal friction of the medium, and  $A$  and  $B$  are elliptic integrals.

Employing *Fürth's* constants  $X_0$  and  $Y_0$ , the integrals  $A$  and  $B$  are connected as follows

$$X_0 = 2ab^2A \quad \text{and} \quad Y_0 = 2ab^2B.$$

#### *c. Calculation of a partition function for the orientation of the ellipsoids relative to time.*

A polar coordinate system  $(\theta, \phi)$  is introduced into the unit sphere with the direction of the field as polar axis. From the origin, we draw for each ellipsoid a radius vector parallel to the momentary direction of the axis of symmetry; hence, for symmetry reasons, the density of the points of intersection on the surface

\*) However, of the same order of magnitude as the migration velocity of electrolyte ions.

of the sphere will statistically depend only on the pole angle  $\theta$ , *i. e.* the angle between the field vector and the axis of symmetry, and furthermore on time, but not on  $\phi$ .

If the relative number of ellipsoids with the axis of symmetry within a solid angle  $d\Omega$  around the direction  $(\theta, \phi)$  is denoted as  $\bar{f} d\Omega$ , the partition function  $f(t, \theta)$  will be altered partly due to the electric field which causes an orientation of the ellipsoids, partly due to the Brownian rotation movements. This alteration of  $f$  may be calculated by a method analogous to that employed by *Debye*, 1929 (76), for the calculation of the orientation of polar molecules in electric fields. Instead of the simple *Maxwell-Boltzmann* partition function which is valid for a statistical equilibrium, only, and on the basis of *Einstein's* theory of the Brownian movements, *P. Debye* derived a partial differential equation which determined the distribution function for the orientation of polar molecules. We shall confine ourselves to a brief outline of this method applied to the present case.

The number of ellipsoids whose direction of major axes in the time interval  $\delta t$  runs more into than out of  $d\Omega$  is given by the equation

$$\delta t \frac{\partial f}{\partial t} d\Omega = \Delta_1 + \Delta_2, \quad (81)$$

where  $\Delta_1$  arises from the orientating effect of the field, and  $\Delta_2$  is caused by the Brownian rotation movements.

If  $\Theta$  is the angle between the axes of  $d\Omega$  and an adjacent solid angle  $d\Omega'$ , the following expression applies

$$\Delta_2 = d\Omega \frac{\overline{\Theta^2}}{4} \left[ \frac{\cos \theta}{\sin \theta} \frac{\partial f}{\partial \theta} + \frac{\partial^2 f}{\partial \theta^2} \right]. \quad (82)$$

From this expression it is evident that the Brownian rotation movements have no influence if  $f$  is independent of  $\theta$ , *i. e.* un-ordered distribution. As soon as an electric field induces an orientation ( $f$  dependent on  $\theta$ ), the Brownian rotation movements influence the distribution.

The rotation moment  $D$ , acting on the individual ellipsoid (*cf.* p. 126) and causing a rotation about an axis normal to the direction of the axis of symmetry and to the field, tends to alter  $\theta$ .

Under the influence of a constant rotation moment, an ellipsoid



will rotate due to friction with a constant angular velocity determined by the equation

$$D = \xi \frac{d\theta}{dt}, \quad (83)$$

where  $\xi$  is the coefficient of resistance already mentioned on page 128. If the rotation moment is positive, the angular velocity is also positive, and *vice versa*. Applying this equation to our case with a variable rotation moment, we shall again assume that the acceleration effect can be neglected. Consequently, we get

$$A_1 = -\frac{\partial}{\partial \theta} \left( 2\pi f \frac{D}{\xi} \sin \theta \right) d\theta. \quad (84)$$

Introducing  $A_1$  and  $A_2$  and  $d\Omega = 2\pi \sin \theta d\theta$  into the original equation, we obtain

$$\frac{\partial f}{\partial t} = \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \left[ \frac{\overline{\Theta^2}}{4\delta t} \frac{\partial f}{\partial \theta} - \frac{D}{\xi} f \right] \right). \quad (85)$$

For the determination of the characteristic constant  $\frac{\overline{\Theta^2}}{\delta t}$  we make use of the fact that in the special case of  $\frac{\partial f}{\partial t} = 0$  (constant field) the *Maxwell-Boltzmann* expression

$$f = A \cdot e^{-\frac{u}{kT}} \quad (86)$$

must be a solution of the differential equation;  $u$  is the potential energy,  $k$  the *Boltzmann* constant (gas constant per single molecule), and  $T$  the absolute temperature. In the stationary case,

$$D = -\frac{\partial u}{\partial \theta}, \quad (87)$$

and consequently it can be shown that the *Maxwell-Boltzmann* expression offers a solution, when

$$\frac{\overline{\Theta^2}}{4\delta t} = \frac{kT}{\xi}. \quad (88)$$

Introducing this expression, we obtain the final differential

equation for the determination of the partition function  $f(t, \theta)$  which then may be found for an arbitrary time dependence of the regulating moment of revolution,

$$\xi \frac{\partial f}{\partial t} = \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \left( kT \frac{\partial f}{\partial \theta} - Df \right) \right]. \quad (89)$$

*d. Solution of the differential equation and determination of the relaxation time of the particles.*

We divide equation (89) by  $kT$  and we transfer the term with  $\frac{\partial f}{\partial \theta}$  to the left side. If the complicated formula for the rotation moment (cf. p. 126) is expressed as

$$D = D_0 \sin 2\theta, \quad (90 \text{ a})$$

$$\tau_0 = \frac{\xi}{kT} \text{ and } \alpha = \frac{2D_0}{kT}, \quad (90 \text{ b, c})$$

where  $\alpha$  may be a function of time, the differential equation for our problem is as follows

$$\tau_0 \frac{\partial f}{\partial t} - \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial f}{\partial \theta} \right] = - \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \sin 2\theta \frac{\alpha}{2} f \right]. \quad (91)$$

Primarily, we consider the homogeneous equation resulting from (91) by putting  $\alpha = 0$ .

$$\tau_0 \frac{\partial f}{\partial t} - \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial f}{\partial \theta} \right] = 0. \quad (92)$$

In the usual way, we assume

$$f \doteq \phi(t) \cdot \psi(\theta), \quad (93)$$

where  $\phi(t)$  is a function of  $t$  alone, and  $\psi(\theta)$  a function of  $\theta$  alone; we get

$$\tau_0 \frac{\phi'}{\phi} = -\lambda = \frac{1}{\psi} \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial \psi}{\partial \theta} \right], \quad (94)$$

where  $\lambda$  is a constant.

Equation (94) may be separated in two equations, one of which, viz.

$$\lambda = -\frac{1}{\psi} \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial \psi}{\partial \theta} \right], \quad (95)$$

is *Legendre's* equation which has admissible solutions only for the Eigenvalues.

$$\lambda = n(n+1) \quad (\text{with } n = 0, 1, 2, \dots). \quad (96)$$

Solutions are the corresponding Eigenfunctions, the normalized spherical harmonics of the first kind

$$\psi_n = \sqrt{\frac{2n+1}{2}} P_n(x) \quad x = \cos \theta. \quad (97)$$

The other part of equation (94) gives

$$\frac{\phi'}{\phi} = -\frac{\lambda}{\tau_0} = -\frac{n(n+1)}{\tau_0} = -\frac{1}{\tau_n} \quad \text{as} \quad \tau_n = \frac{\tau_0}{n(n+1)}. \quad (98)$$

The solution of this equation is

$$\phi_n = C_n e^{-\frac{t}{\tau_n}}. \quad (99)$$

Hence, the general solution of (92) is

$$f = \sum_{n=0}^{\infty} C_n \psi_n(\cos \theta) e^{-\frac{t}{\tau_n}} = \sum_{n=0}^{\infty} C_n \psi_n(\cos \theta) e^{-\frac{n(n+1)t}{\tau_0}}. \quad (100)$$

By a suitable choice of the coefficients  $C_n$ , this solution may be adapted to any function at the time  $t = 0$ , and we see that independent of the initial conditions, we obtain in the course of time an equal distribution, since all terms except the first one are eliminated, and  $P_0(x) = 1$ .

$f(t, \theta)$  is given at the time  $t = 0$ , for example  $f(0, \theta) = F(\theta)$ , where  $F$  is a given function

$$F(\theta) = \sum_{n=0}^{\infty} C_n \psi_n(\cos \theta). \quad (101)$$

In order to solve (91) with this initial condition, we carry out a calculation of perturbation, considering  $a$  to be a small value;

$$f = f^0 + f^1, \quad (102)$$

where  $f^0$  is that solution of the homogeneous equation (92) which at  $t = 0$  is equal to the assumed  $f$  at  $t = 0$ . In other words,  $f^1 = 0$  at  $t = 0$  for all  $\theta$ ; and, consequently,  $f^0$  is a given known function.

As both  $\alpha$  and  $f^1$  are small, the products are disregarded so that substitution of (102) in (91) leads to

$$\tau_0 \frac{\partial f^1}{\partial t} - \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial f^1}{\partial \theta} \right] = -\frac{1}{2} \frac{\alpha}{\sin \theta} [\sin \theta \sin 2 \theta f^0]. \quad (103)$$

(103) is a non-homogeneous differential equation whose right side is a given function of  $f^0$  and  $\theta$ .

For any time  $t$ , we may expand  $f^1(t, \theta)$  in terms of the Eigenfunctions of the homogeneous equation

$$f^1(t, \theta) = \sum_{n=0}^{\infty} \phi_n^1(t) \psi_n(\cos \theta). \quad (104)$$

Substitution of (104) into (103) gives for the left side

$$\begin{aligned} & \tau_0 \sum_{n=0}^{\infty} \frac{d\phi_n^1(t)}{dt} \psi_n(\cos \theta) - \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial}{\partial \theta} \sum_{n=0}^{\infty} \phi_n^1(t) \psi_n(\cos \theta) \right] = \\ & \tau_0 \sum_{n=0}^{\infty} \frac{d\phi_n^1(t)}{dt} \psi_n(\cos \theta) - \sum_{n=0}^{\infty} \phi_n^1(t) \underbrace{\frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left[ \sin \theta \frac{\partial \psi_n(\cos \theta)}{\partial \theta} \right]}_{-n(n+1)\psi_n(\cos \theta)} \end{aligned} \quad (105)$$

and the whole equation becomes

$$\begin{aligned} & \sum_{n=0}^{\infty} \left[ \tau_0 \frac{d\phi_n^1(t)}{dt} + n(n+1)\phi_n^1(t) \right] \psi_n(\cos \theta) = \\ & -\frac{\alpha}{2 \sin \theta} \frac{\partial}{\partial \theta} [\sin \theta \sin 2 \theta f^0]. \end{aligned} \quad (106)$$

If we introduce  $x = \cos \theta$  as a new variable instead of  $\theta$ , we finally get

$$\sum_{n=0}^{\infty} \left[ \tau_0 \frac{d\phi_n^1(t)}{dt} + n(n+1)\phi_n^1(t) \right] \psi_n(x) = + \alpha \frac{d}{dx} [x(1-x^2)f^0]. \quad (107)$$

After multiplication of this equation by  $\psi_m(x)$  and integration over  $x$  from  $-1$  to  $+1$ , employing the orthogonal relations of spherical harmonics,

$$\int_{-1}^{+1} \psi_n(x) \psi_m(x) dx = 0 \quad \text{and} \quad \int_{-1}^{+1} [\psi_m(x)]^2 dx = 1 \quad (108)$$

$n \neq m$   $n = m$

we get

$$\tau_0 \frac{d\phi_m^1(t)}{dt} + m(m+1)\phi_m^1(t) = g_m(t), \quad (109)$$

where

$$g_m(t) = +a \int_{-1}^{+1} \psi_m(x) \frac{d}{dx} [x(1-x^2)f^0(t, x)] dx, \quad (110)$$

and  $m = 0, 1, 2, 3, \dots, \infty$ .

In order to solve (109), using again index  $n$  instead of  $m$ , we put

$$\phi_n^1(t) = e^{-\frac{t}{\tau_n}} y_n(t) = e^{-\frac{n(n+1)t}{\tau_0}} y_n(t). \quad (111)$$

By substitution, we get

$$\tau_0 \frac{dy_n(t)}{dt} = g_n(t) e^{-\frac{t}{\tau_n}}. \quad (112)$$

(112) may be integrated directly, since  $y_n$ , like  $\phi_n^1$  and  $f^1$ , will vanish when  $t = 0$ . We obtain

$$y_n(t) = \frac{1}{\tau_0} \int_0^t g_n(t') e^{\frac{t'}{\tau_n}} dt', \quad (113)$$

where  $t'$  is a variable of integration, or according to (111),

$$\phi_n^1(t) = \frac{1}{\tau_0} e^{-\frac{t}{\tau_n}} \int_0^t g_n(t') e^{\frac{t'}{\tau_n}} dt'. \quad (114)$$

Substituting this expression into (104), we get  $f^1$  as a function of  $t$  and  $x$ , or of  $t$  and  $\theta$ .

The general formulas so far derived will now be applied to a particular, but simple initial distribution.

If  $f$  at the time  $t = 0$  is independent of  $\theta$ , we have  $f^0 = 1$  for  $t = 0$ ; and since  $f^0 = \text{constant}$  is a solution of the homogeneous equation,  $f^0 = 1$  is valid for all  $t$ .

For  $g_n(t)$  we find

$$g_n(t) = + \alpha(t) \int_{-1}^{+1} \psi_n(x) (1 - 3x^2) dx. \quad (115)$$

However, we know that

$$P_2(x) = \frac{1}{2} (3x^2 - 1) \text{ and } \psi_2 = \sqrt{\frac{5}{2}} P_2(x). \quad (116)$$

Therefore,

$$g_n(t) = -2 \sqrt{\frac{2}{5}} \alpha(t) \int_{-1}^{+1} \psi_n(x) \psi_2(x) dx. \quad (117)$$

Hence, for this simple initial condition (equal distribution of direction), all  $g_n(t) = 0$ , except  $g_2(t)$  which is equal to  $-2 \sqrt{\frac{2}{5}} \alpha(t)$ .

This means  $\phi_n^1(t) = 0$  for all  $n \neq 2$ , and

$$\phi_2^1(t) = -\frac{1}{\tau_0} e^{-\frac{t}{\tau_0}} \int_0^t 2 \sqrt{\frac{2}{5}} \alpha(t') e^{\frac{t'}{\tau_0}} dt'. \quad (118)$$

If we consider, furthermore, the case that a constant field is applied at the time  $t = 0$ ,  $\alpha$  becomes constant in the time, and we obtain

$$\phi_2^1(t) = -2 \sqrt{\frac{2}{5}} \alpha \left(1 - e^{-\frac{t}{\tau_0}}\right) \frac{1}{6}, \quad (119)$$

since

$$\int_0^t e^{\frac{t'}{\tau_0}} dt' = \tau_0 \left(e^{\frac{t}{\tau_0}} - 1\right) \text{ and } \tau_2 = \frac{1}{6} \tau_0. \quad (120)$$

As

$$f^1 = \phi_2^1(t) \psi_2(\cos \theta), \text{ and } \psi_2(\cos \theta) = \frac{1}{2} \sqrt{\frac{5}{2}} (3 \cos^2 \theta - 1) \quad (121)$$

we get

$$f = f^0 + f^1 = 1 - \frac{\alpha}{6} \left(1 - e^{-\frac{t}{\tau_0}}\right) (3 \cos^2 \theta - 1). \quad (122)$$

With  $t = \infty$ , formula (122) represents the simple *Maxwell* distribution because, in this case, we get

$$f = 1 - \frac{\alpha}{4} \left( \cos 2\theta + \frac{1}{3} \right). \quad (123)$$

This means that, apart from the values of higher orders of  $\alpha$ , we have

$$f \sim e^{-\frac{\alpha}{4} \left( \cos 2\theta + \frac{1}{3} \right)} \sim \text{const } e^{-\frac{\alpha}{4} \cos 2\theta} \sim \text{const } e^{-\frac{u}{kT}}, \quad (124)$$

where

$$\alpha = \frac{2D_0}{kT} \quad \text{and} \quad D = D_0 \sin 2\theta = -\frac{\partial u}{\partial \theta}, \quad (125)$$

as an integration of the last expression leads to

$$u = \frac{D_0}{2} \cos 2\theta = \frac{\alpha}{4} kT \cos 2\theta. \quad (126)$$

The relaxation time of the particles derived from (122) is

$$\tau_2 = \frac{\tau_0}{6} = \frac{\xi}{6kT}. \quad (127)$$

If  $\alpha$  is a function of time  $\alpha(t)$  (for example, if the field results from a sine potential), and the usual symbols for maximum amplitude, angular velocity, and phase shift are applied, we get

$$E = E_0 \sin(\omega t + \delta), \quad \text{and} \quad D = D_0 \sin 2\theta \sin^2(\omega t + \delta)$$

$$D_0 \sin^2(\omega t + \delta) = D_0 \left[ \frac{e^{i(\omega t + \delta)} - e^{-i(\omega t + \delta)}}{2i} \right]^2 = \quad (128)$$

$$\frac{D_0}{2} - \frac{D_0}{2} \text{Real part of } \left\{ e^{i(2\omega t + 2\delta)} \right\}$$

i. e.

$$\alpha(t) = \frac{2D_0 \sin^2(\omega t + \delta)}{kT} = \frac{D_0}{kT} - \frac{D_0}{kT} R \left\{ e^{i(2\omega t + 2\delta)} \right\}. \quad (129)$$

Introducing this  $\alpha(t)$  into expression (118) previously found for  $\phi_2^1(t)$ , and remembering that

$$f^1 = \phi_2^1(t) \psi_2(\cos \theta), \quad (130)$$

rather simple calculations lead to

$$f = f^0 + f^1 = 1 - \frac{D_0}{6kT} (3 \cos^2 \theta - 1) \left\{ 1 - \frac{\cos[2\omega t + 2\delta] + 2\omega\tau_2 \sin[2\omega t + 2\delta]}{1 + (2\omega\tau_2)^2} - e^{-\frac{t}{\tau_2}} \left[ 1 - \frac{\cos[2\delta] + 2\omega\tau_2 \sin[2\delta]}{1 + (2\omega\tau_2)^2} \right] \right\} \quad (131 a)$$

$$f = 1 - \frac{D_0}{6kT} (3 \cos^2 \theta - 1) \left\{ 1 - \frac{1}{\sqrt{1 + (2\omega\tau_2)^2}} \cos[2\omega t + 2\delta + b] - e^{-\frac{t}{\tau_2}} \left[ 1 - \frac{1}{\sqrt{1 + (2\omega\tau_2)^2}} \cos[2\delta + b] \right] \right\} \quad (131 b)$$

$$f = 1 - \frac{D_0}{6kT} (3 \cos^2 \theta - 1) G(t), \quad (131 c)$$

where  $b = \arctan(-2\omega\tau_2)$  signifies a phase shift, and  $G(t)$  an abbreviation of the  $\{\}$  parenthesis.

Hence, the distribution of direction varies with twice the frequency of the field intensity, which is easy to understand, since the rotation moment (*cf.* p. 126) depends on the square of the field intensity.

If  $\omega = 0$   $\delta = \frac{\pi}{2}$ , we get  $G(t) = 2 \left( 1 - e^{-\frac{t}{\tau_2}} \right)$  and  $f$  becomes equal to expression (122) with  $a \text{ const} = \frac{2D_0}{kT}$ .

If  $(\omega\tau_2) \gg 1$ , we get

$$f = 1 - \frac{D_0}{6kT} (3 \cos^2 \theta - 1) \left( 1 - e^{-\frac{t}{\tau_2}} \right) = 1 - \frac{a}{12} (3 \cos^2 \theta - 1) \left( 1 - e^{-\frac{t}{\tau_2}} \right); \quad (132)$$

*i. e.* when the oscillation periods are small compared with the time of relaxation, the expression for the deviation from the equal distribution is exactly half the corresponding expression for direct current.

*e. Calculation of the conductivity of a suspension at a given time.*

*H. Fricke*, 1924 (132), calculated the conductivity of a suspension of ellipsoids assuming a random orientation of the ellipsoids.

Since we are mainly interested in the influence of the orientating effect of the electric field on the conductivity of the suspension, his method should be generalized.



We consider again (*cf.* p. 126) a fixed coordinate system  $x, y, z$  in the ellipsoid, whose  $x$ -axis overlaps the axis of symmetry and whose  $z$ -axis is normal to the direction of the applied external electric field. Furthermore, we introduce the coordinate system  $x', y', z'$ , the point of origin and the  $z$ -axis being common for both systems, while the  $x'$ -axis falls in the direction of the field.

The components of the applied field in the directions of the  $x$ -,  $y$ -, and  $z$ -axes are

$$E_x = E \cos \theta \quad E_y = E \sin \theta \quad E_z = 0, \quad (133)$$

where  $\theta$ , as previously, denotes the acute angle between the axis of symmetry ( $x$ -axis) and the direction of the field ( $x'$ -axis).

For the components of the field intensity inside an ellipsoid in the directions of the principal axes ( $x, y, z$ ), we have (*cf.* Fürth, 1924 (140) )

$$E'_x = -\frac{\partial \phi}{\partial x} = -\alpha_1 \quad E'_y = -\frac{\partial \phi}{\partial y} = -\beta_1 \quad E'_z = -\frac{\partial \phi}{\partial z} = -\gamma_1, \quad (134)$$

where

$$\begin{aligned} \alpha_1 &= -\frac{E_x}{1 + \frac{\mu-1}{4} X_0} = -\frac{E \cos \theta}{1 + \frac{\mu-1}{4} X_0} \\ \beta_1 &= -\frac{E_y}{1 + \frac{\mu-1}{4} Y_0} = -\frac{E \sin \theta}{1 + \frac{\mu-1}{4} Y_0} \\ \gamma_1 &= -\frac{E_z}{1 + \frac{\mu-1}{4} Z_0} = -\frac{0}{1 + \frac{\mu-1}{4} Z_0} = 0, \end{aligned} \quad (135)$$

and

$$\begin{aligned} X_0 &= 2ab^2 \int_0^\infty \frac{dt}{(\alpha^2 + t) T(t)} \quad Y_0 = 2ab^2 \int_0^\infty \frac{dt}{(b^2 + t) T(t)} \\ T(t) &= \sqrt{\alpha^2 + t} (b^2 + t). \end{aligned} \quad (136)$$

The  $x'$  component of the intensity of the field inside the ellipsoid  $E'_x$  can be calculated by means of the formula

$$A_s = A_x \cos(s, x) + A_y \cos(s, y) + A_z \cos(s, z), \quad (137)$$

and we obtain

$$E'_x = -a_1 \cos \theta - \beta_1 \sin \theta = \frac{E \cos^2 \theta}{1 + \frac{\mu-1}{4} X_0} + \frac{E \sin^2 \theta}{1 + \frac{\mu-1}{4} Y_0}. \quad (138)$$

The intensity of the field outside the ellipsoids will be denoted as  $\underline{E}^\circ$ . In the immediate proximity of the ellipsoid  $\underline{E}^\circ$  deviates from  $E$ , but at great distances from the ellipsoids the two values are identical.

The volume between the electrodes is termed  $\Omega$ , and the total volume of the ellipsoids is denoted as  $\Omega_1$ .

$F_0$  be the intensity of the electric field at an arbitrary point of the suspension medium. For a definite given distribution and orientation of the ellipsoids, we form the mean value over the space outside the ellipsoids, and we denote this mean value as

$$\underline{F} = \overline{F_0} \Big|_{\text{outside ellipsoids}}. \quad (139)$$

We know that it is a vector normal to the electrodes; hence

$$F_{x'} = F \text{ and } F_{y'} = F_{z'} = 0. \quad (140)$$

Inside the ellipsoids, we have a given field intensity  $\underline{F}_i$  which, strictly speaking, varies from point to point.

Considering all ellipsoids whose axes of symmetry ( $x$ -axis) form an angle between  $\theta$  and  $\theta + d\theta$  with the direction of the field ( $x'$ -axis), and forming the mean value of  $\underline{F}_i$  over the volume of these ellipsoids, we arrive at a vector  $\underline{F}_i(\theta)$ , viz.

$$\underline{F}_i(\theta) = \overline{F_i} \Big|_{\theta, \theta + d\theta}. \quad (141)$$

It is natural to assume that this mean field intensity  $\underline{F}_i(\theta)$  is the same as the constant field in a single ellipsoid which is placed in a suitable external constant field  $\underline{E}$ , and whose axis of symmetry forms the angle  $\theta$  with the direction of this field.

The problem remains how to choose this field  $\underline{E}$ . The mean value of  $\underline{E}^\circ$  (cf. above) taken over a volume ( $\Omega - \Omega_1$ ) outside the ellipsoid must be equal to the  $\underline{F}$  found above.

If the volume  $\Omega$  is great compared with the volume of a single ellipsoid, the mean value of  $\underline{E}^\circ$  within this region is approximately equal to  $\underline{E}$  and, therefore, we have to put

$$\underline{E} = \underline{F} \text{ and } \underline{E}' = F_i(\theta) \quad (142)$$

$E'_x$ , etc. being the components of  $\underline{F}_i(\theta)$ .

In order to find a relation between  $\underline{F}$  and  $V$  (the potential between the electrodes), we realize that the mean value of the real field intensity taken over the whole volume  $\Omega$  must be equal to  $\frac{V}{l}$ , where  $l$  is the distance between the plates, i. e.

$$\overline{(F_o)_x} \Big|_{\text{outside ellipsoids}} (\Omega - \Omega_1) + \overline{(F_i)_x} \Big|_{\text{inside ellipsoids}} \Omega_1 = \frac{V}{l} \Omega \quad (143)$$

which is equal to

$$F(\Omega - \Omega_1) + \Omega_1 \int_{\theta=0}^{\theta=\pi} (F_i(\theta))_x N(\theta) d\theta = \frac{V}{l} \Omega, \quad (144)$$

where  $N(\theta) d\theta$  is the relative number of ellipsoids within  $\Omega$  whose axis of symmetry forms an angle between  $\theta$  and  $\theta + d\theta$  with the  $x'$ -axis, and is normalized so that

$$\int_0^\pi N(\theta) d\theta = 1. \quad (145)$$

Applying (138) and (142), we get instead of (144)

$$(\Omega - \Omega_1) F + \Omega_1 F \int_0^\pi \left\{ \frac{\cos^2 \theta}{1 + \frac{\mu-1}{4} X_0} + \frac{\sin^2 \theta}{1 + \frac{\mu-1}{4} Y_0} \right\} N(\theta) d\theta = \frac{V}{l} \Omega. \quad (146)$$

This relation replaces *Fricke's* equation 7, (1924 (132, p. 580)).

If  $\rho$  denotes the volume concentration  $\rho = \frac{\Omega_1}{\Omega}$ , and we divide (146) by  $\Omega$ , we get

$$F(1 - \rho) + \rho F \int_0^\pi \left\{ \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right\} N(\theta) d\theta = \frac{V}{l}, \quad (147)$$

where

$$A = 1 + \frac{\mu-1}{4} X_0 \quad B = \frac{\mu-1}{4} Y_0. \quad (148)$$

When the mean value of the field intensity is known, we also know the mean value of the density of the current  $u$ , since

$$\underline{u} = \sigma \underline{E} \quad (149)$$

applies to every point, so that the mean value of  $\underline{u}$  in a region where  $\sigma$  is constant is equal to  $\sigma$  times the mean value of the field intensity.

For the mean value of  $\underline{u}$  outside the ellipsoids we, therefore, get

$$\underline{u}^0 = \overline{\underline{u}_o} \Big|_{\text{outside ellipsoids}} = \sigma^0 \overline{\underline{F}_o} \Big|_{\text{outside ellipsoids}} = \sigma^0 \underline{F}. \quad (150)$$

$u^\circ$  is normal to the electrodes and is equal to  $\sigma^\circ \underline{F}$ .

The mean value of the  $x'$ -component of the current density inside the ellipsoids, where the direction of the axes of symmetry lies between  $\theta$  and  $\theta + d\theta$ , is likewise

$$\begin{aligned} (u_i(\theta))_{x'} &= \sigma (F_i(\theta))_{x'} = \sigma E'_{x'} = \sigma \underline{E} \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right) \\ &= \sigma F \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right). \end{aligned} \quad (151)$$

Hence, the mean value of the  $x'$ -component of the current density over the whole region  $\Omega$  becomes equal to

$$\sigma^0 \underline{F} (\Omega - \Omega_1) + \Omega_1 \int_0^\pi \sigma F \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right) N(\theta) d\theta = \bar{u}_{x'} \Omega \quad (152)$$

$$\sigma^0 F (1 - \rho) + \rho \sigma F \int_0^\pi \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right) N(\theta) d\theta = \bar{u}_{x'}. \quad (153)$$

The conductivity of the suspension  $\sigma_m$  is defined by the equation

$$\bar{u}_{x'} = \sigma_m \frac{V}{l}. \quad (154)$$

We put

$$I = \int_0^\pi \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right) N(\theta) d\theta \quad (155)$$

and, instead of (147) and (153), we get

$$F(1 - \rho) + \rho FI = \frac{V}{l} \quad \text{and} \quad (156)$$

$$\sigma^0 F(1 - \rho) + \sigma \rho FI = \sigma_m \frac{V}{l}, \quad \text{which gives} \quad (157)$$

$$\sigma_m = \frac{\sigma^0 + \rho(\sigma I - \sigma^0)}{1 + \rho(I - 1)}. \quad (158)$$

Obviously, the relative number of ellipsoids whose direction of the axes of symmetry falls between  $\theta$  and  $\theta + d\theta$  is proportional to  $f(\theta) \sin \theta d\theta$  and, hence,

$$N(\theta) d\theta = C f(\theta) \sin \theta d\theta, \quad (159)$$

where the constant  $C$  can be determined by the normalizing equation

$$\int_0^\pi N(\theta) d\theta = \int_0^\pi C f(\theta) \sin \theta d\theta = 1. \quad (160)$$

The function  $f(\theta)$  is normalized so that the integral extended over all directions is equal to  $4\pi$ , since we proceeded from an equal distribution; this integral is constant with time, *i. e.*

$$4\pi = \int_{\text{sphere of unit.}} f(\theta) d\Omega = \int_0^{2\pi} \int_0^\pi f(\theta) d\phi \sin \theta d\theta = 2\pi \int_0^\pi f(\theta) \sin \theta d\theta. \quad (161)$$

This means that  $C = \frac{1}{2}$  or

$$N(\theta) d\theta = \frac{1}{2} f(\theta) \sin \theta d\theta, \quad (162)$$

and thus we get

$$I = \int_0^\pi \left( \frac{\cos^2 \theta}{A} + \frac{\sin^2 \theta}{B} \right) \frac{1}{2} f(\theta) \sin \theta d\theta. \quad (163)$$

If we introduce  $x = \cos \theta$  as a new variable of integration, we find

$$I = - \int_{+1}^{-1} \left( \frac{x^2}{A} + \frac{1-x^2}{B} \right) \frac{1}{2} f(x) dx. \quad (164)$$

For an equal distribution of direction,  $f = f^0 = 1$ ; the corresponding  $I$  is denoted as

$$I_0 = \frac{1}{2} \int_{-1}^{+1} \left( \frac{x^2}{A} + \frac{1-x^2}{B} \right) dx = \frac{1}{3} \left( \frac{1}{A} + \frac{2}{B} \right). \quad (165)$$

This value introduced in (158) gives  $\sigma_m$  for a random distribution of direction, in agreement with *H. Fricke*, 1924 (132).

For  $\alpha$  independent of time  $t$  ( $\omega \rightarrow 0$ ) we found earlier (cf. p. 135)

$$f = 1 - \frac{\alpha}{6} (3 \cos^2 \theta - 1) \left( 1 - e^{-\frac{t}{\tau_1}} \right). \quad (166)$$

Introducing again  $x = \cos \theta$  as a variable of integration, we find for the corresponding  $I$

$$\begin{aligned} I_{\alpha \text{ const.}} &= I_0 - \frac{\alpha}{4} \left( 1 - e^{-\frac{t}{\tau_1}} \right) \int_{-1}^{+1} \left( \frac{x^2}{A} + \frac{1-x^2}{B} \right) \left( x^2 - \frac{1}{3} \right) dx \\ &= I_0 - \frac{2\alpha}{45} \left( 1 - e^{-\frac{t}{\tau_1}} \right) \left( \frac{1}{A} - \frac{1}{B} \right). \end{aligned} \quad (167)$$

We see that  $I$  decreases from the value  $I_0$  at the initial state of equal distribution to the value  $I_{\alpha \text{ const.}}$

The time of relaxation — i. e. the time which passes until the conductivity attains its new constant value — is  $\tau_2 = \frac{\tau_0}{6}$  as already stated on p. 136.

In the case of  $\sigma_0 \gg \sigma I$ , equation (158) reveals that a decrease in  $I$  indicates an increase in conductivity in the course of time.

If, however,  $\sigma$  is so great compared with  $\sigma_0$  that  $\sigma_0$  can be considered small relative to  $\sigma I$ , a decrease in  $I$  indicates a decrease in the conductivity of the suspension.

For  $\alpha$  dependent on time,  $\alpha(t)$ , we found (cf. formula 131c, p. 137)

$$f = 1 - \frac{\alpha}{4} \left( x^2 - \frac{1}{3} \right) G(t). \quad (168)$$

The corresponding  $I$  becomes

$$\begin{aligned} I_{\alpha(t)} &= I_0 - \frac{\alpha}{8} G(t) \int_{-1}^{+1} \left( \frac{x^2}{A} + \frac{1-x^2}{B} \right) \left( x^2 - \frac{1}{3} \right) dx \\ &= I_0 - \frac{\alpha}{45} \left\{ \frac{1}{A} - \frac{1}{B} \right\} \left\{ 1 - \frac{1}{\sqrt{1 + (2\omega\tau_2)^2}} \cos [2\omega t + 2\delta + b] \right. \\ &\quad \left. - e^{-\frac{t}{\tau_1}} \left[ 1 - \frac{1}{\sqrt{1 + (2\omega\tau_2)^2}} \cos [2\delta + b] \right] \right\}. \end{aligned} \quad (169)$$

For  $(\omega \tau_2) \gg 1$  we get

$$I_{\alpha(t)} = I_0 - \frac{\alpha}{45} \left( \frac{1}{A} - \frac{1}{B} \right) \left( 1 - e^{-\frac{t}{\tau_2}} \right), \quad (170)$$

where the term containing  $\alpha$  is half the corresponding term in the expression for  $I_{\alpha \text{ const.}}$ .

*f. Numerical examples of the preceding calculations.*

The effect of orientation especially depends upon the most characteristic term of our theory, *viz.*

$$\alpha = \frac{2D_0}{kT} \left( \sim \frac{\text{field energy per ellipsoid}^*)}{kT} \right), \quad (171)$$

*i. e.* on  $\epsilon_0$ ,  $E$ ,  $\mu = \frac{\sigma}{\sigma_0}$ ,  $a$ ,  $b$  and  $T$ , ( $X_0$  and  $Y_0$  depend only on  $\kappa = \frac{b}{a}$ ,  $\lambda$  also on  $a$ ;

$$I_0 = \frac{1}{3} \left( \frac{1}{A} + \frac{2}{B} \right) \quad \text{and} \quad \left( \frac{1}{A} - \frac{1}{B} \right) \quad (172)$$

depend on  $\mu$  and  $\kappa$ ) besides, furthermore, on the volume concentration  $\rho$  (formula (158), p. 142).

The duration of the effect is determined by the time of relaxation

$$\tau_2 = \frac{\xi}{6kT} \quad (173)$$

which depends on  $\eta$  and, moreover, on  $a$ ,  $b$ , and  $T$ .

The formula for the rotation moment  $D$  (*cf.* formula 77, p. 126) shows clearly that we have to distinguish between two main cases, *viz.*

I.  $\mu \gg 1$ , and II.  $\mu \ll 1$ . In the first case, we may obtain considerable effects; in the second case, however, the effect will be insignificantly small, since the magnitude of the denominator of the expression for  $D$  mainly depends on  $\mu$ .

For the sake of simplicity, examples are calculated for rod-shaped particles (prolate ellipsoids of revolution), only.

$$\begin{array}{lll} \text{I. } \mu \gg 1 & \sigma = 1 \cdot 10^{-4} \text{ ohm}^{-1} \text{ cm}^{-1} & a = 4 \cdot 10^{-4} \text{ cm} \\ & \sigma_0 = 1 \cdot 10^{-6} \text{ ohm}^{-1} \text{ cm}^{-1} & b = 0.5 \cdot 10^{-4} \text{ cm} \end{array}$$

\*) For  $D_0$ , *cf.* formula 90 a, p. 131.

$$\mu = \frac{\sigma}{\sigma_0} = 100 \quad \kappa = \frac{b}{a} = \frac{1}{8} \quad T = 291^\circ \text{ Kelvin } (18^\circ \text{C}).$$

Sine voltage 1000 cycles.  $E_0 = \text{maximum voltage/cm} = 2 \text{ volts/cm}$   
 $= \frac{2}{300} \text{ electrostatic units/cm.}^*)$

$$a = -2.4284. \quad I_{\alpha \text{ const.}} = 0.26358 + 0.03939 \cdot \left(1 - e^{-\frac{t}{\tau_1}}\right).$$

For  $\eta = 0.05$  Poise, we have  $\tau_2 = 159.4$  seconds.

We calculate  $I_{\alpha \text{ const.}}$  and introduce this value into formula (158). In this way, the conductivity at different times is obtained.

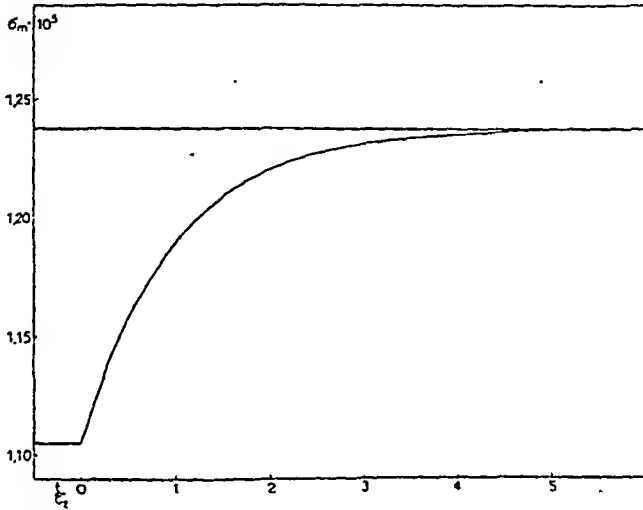


Fig. 3. "Orientation effect" of a suspension of ellipsoidal particles (*cf.* the text).

Ordinates: specific conductivity  $\sigma_m (\cdot 10^5)$ .

Abscissae: time  $t$  in multiples of the time of relaxation of the particles ( $t/\tau_2$ ).

Fig. 3 exhibits the orientation effect when the volume concentration of the suspension,  $\rho$ , is equal to 0.3, *i. e.*

$$\frac{\rho}{\frac{4}{3} ab^2 \pi} = \text{about } 7 \cdot 10^{10} \text{ particles/cc.}$$

$$\text{II. } u \ll 1 \quad \sigma = 1 \cdot 10^{-6} \text{ ohm}^{-1} \text{ cm}^{-1} \quad a = 4 \cdot 10^{-4} \text{ cm}$$

$$\sigma_0 = 1 \cdot 10^{-4} \text{ ohm}^{-1} \text{ cm}^{-1} \quad b = 0.5 \cdot 10^{-4} \text{ cm}$$

$$\mu = \frac{1}{100} \quad \kappa = \frac{1}{8} \quad T = 291^\circ \text{ Kelvin } (18^\circ \text{C}).$$

\*) *Cf.* formula 128, p. 136.



Sine voltage, 1000 cycles,  $E_0 = \text{maximum voltage/cm} = \frac{2}{300}$  electrostatic units/cm.

$\alpha = -0.03226$ .  $I_{\alpha(t)} = 1.6502 - 0.0007 \left(1 - e^{-\frac{t}{\tau_2}}\right)$ . For  $\eta = 0.05$  Poise, we have  $\tau_2 = 159.4$  seconds.

In this case, the orientation effect becomes negligible, as the conductivity increases only from  $5.8987 \cdot 10^{-5}$  to  $5.8996 \cdot 10^{-5}$  ohm $^{-1}$  cm $^{-1}$ , i. e.  $0.0009 \cdot 10^{-5}$  ohm $^{-1}$  cm $^{-1}$  from time 0 to time  $\infty$ .

The slight rotation moment in case II explains why *Freundlich* and *Abramson*, 1928 (127), and *Abramson*, 1928 (2), in cataphoresis experiments did not find any orientation of horse blood corpuscles (which may almost be considered oblate ellipsoids of revolution), neither when situated separately nor in rouleaux ("piles of coins").

On account of the completely negligible orientation in the case of erythrocytes, an influence on the conductivity cannot be noticed, so that *H. Fricke's* formula (or formula (158) p. 142 with the introduction of  $I_0$ , p. 142) which assumes a random direction distribution of the corpuscles must be regarded as correct. Moreover, the orientation effect will involve an increase in conductivity of the blood corpuscle suspension, in contrast to the observed conductivity effect (cf. p. 94) which indicates a decrease in conductivity.

As  $D$  depends on  $a^3$ , the orientation effect will be very slight for very small particles, even in case I ( $\mu \gg 1$ ).

In the experiment performed by *Kruyt*, 1916 (233), with a colloidal solution of vanadium pentoxide ( $\alpha = 0.5 \mu$ ), it must therefore be assumed that the particles are orientated due to endosmotic flow in the very shallow observation chamber (*ceteris paribus*, if  $\alpha$  decreases from  $4 \cdot 10^{-4}$  to  $0.5 \cdot 10^{-4}$ ,  $D$  will be reduced by  $64/0.125 = 512$  times).

The different views held by French physicists (*Cotton* and *Mouton*, *Meslin* and *Chaudier*) and by German colloid chemists (*Freundlich* and collaborators, *Kruyt*) concerning the cause of the orientation of particles due to "electric double refraction" in suspensions have been discussed by *C. E. Marshall*, 1930 (272). *Th. Wereide*, 1927 (435), studied experimentally the electric double refraction of Benzopurpurin sols.

### § 38. A NEW THEORY OF ROULEAUX FORMATION OF THE RED BLOOD CORPUSCLES.

The founder of colloid chemistry, *Thomas Graham*, 1864 (157, p. 184), emphasized: "The colloidal is, in fact, a dynamical state of matter, the crystalloidal being the statical condition. The colloid *possesses Energia*. It may be looked upon as the probable primary source of the force appearing in the phenomena of vitality". Even if rouleaux formation of blood corpuscles is no directly vital phenomenon, this process is in some respect a symbol of *Graham's* interpretation.

On account of the experimental difficulties of a direct measurement of intercorpuscular forces (*cf.* theory, § 34, p. 105, and experiments, § 41, p. 169), it might be attempted whether calculations on the basis of a suitable aggregation hypothesis lead to a quantitative interpretation of coagulation forces. However, a hypothesis of this kind accessible to the instrument of the theoretical physicist is missing until now.

The previous discussion of the literature concerning aggregation theories (*cf.* § 18, p. 34) did not bring us any further to a concrete interpretation of the mechanism of rouleaux formation, except for the important result that *an increased tendency to aggregation is accompanied by an increased electrokinetic potential*; also the transcription assuming a hydration of the erythrocyte surface covers only a very modest knowledge.

Owing to essential works from the field of the theory of strong electrolytes and the ensuing attempts to apply this theory to the colloidal state, it has become possible to give a physical explanation of rouleaux formation. *The author's theory which is based upon the electrostatic cohesion pressure assumes — in contradistinction to earlier theories, especially the critical potential theory (§ 25, p. 64) — the electric double layer of the particles (§ 23, p. 57) to be the cause of attraction.*

With increasing pressure, a real gas reduces its volume more than corresponds to the equation of state of an ideal gas  $P V = R T$ . According to *J. D. van der Waals*, 1899 (429), the increased compression corresponds to an extra pressure (cohesion pressure) caused by the attractive forces between the molecules of the gas. In analogy to *van der Waals'* theory, solutions of strong electrolytes show a cohesion pressure produced by electrostatic

forces. This pressure acts analogously to the normal cohesion pressure, producing a lowering of the osmotic pressure relative to that given by the equation  $P V = R T$ .\*) In contrast to *van der Waals'* molecular forces which, due to their short range of action, affect only the molecules in the immediate proximity, the *Coulomb* forces — decreasing much slower with the distance — also cause a coupling with more distant ions. In this way, the electrolyte gets a structure, since the ions are surrounded by the *Milner-Debye* ionic atmosphere (1912 (277) and 1921 (74)); hence, during a longer interval we find on average an excess of ions of opposite sign round the central ion.

*A central ion or a colloidal particle with its ionic atmosphere forms a mechanical system in which electrostatic forces act between the single components.* For the distribution of electric charges, *W. Thomson's* well-known electrostatic principle holds (*W. Thomson*, 1848 (413), *J. C. Maxwell*, 1881 (273)). If the charges in an electrostatic field move under the action of the field strength, the energy of the field decreases proportional to the magnitude of the work performed. *If freely movable, the charges will therefore tend to attain such a distribution that the field energy is reduced to a minimum.* This minimal principle which, among others, is treated in the so-called calculus of variation, corresponds to the equilibrium condition of heavy bodies in a gravitational field so that the electric energy plays the same part as the potential energy in ordinary mechanics (*R. Courant* and *D. Hilbert*, 1931 (71), *R. Becker*, 1933 (20)).

In order to ascertain equilibrium in the above mentioned mechanical systems *at rest*, it is therefore sufficient to investigate whether the potential energy has a minimum value at possible infinitesimal displacements.

*The potential energy\*\*\*) of a central ion relative to its ionic at-*

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\*) *Addendum:* By isothermal compression of the electrolyte solution by means of a semi-permeable, frictionless piston, work is performed which is minor than the ideal work. The difference represents a reduction of the free energy of that part of the solution which originates from electrostatic forces. (*A. Eucken*, *Lehrbuch der chemischen Physik*. Akad. Verlagsges., Leipzig, 1930, p. 399).

\*\*) *Addendum:* Since the energy alterations of the electric field due to polarization (*i. e.* unequal distribution of charges) do not occur adiabatically but isothermally, and the surroundings serve as a heat reservoir, we should exactly speaking reckon with free energy in a thermodynamical sense, instead of potential energy (*cf. R. Becker* (20, I. p. 22), *N. Bjerrum*, *Z. phys. Chem.* 119, 145, 1926, and *S. Levine*, *Proc. Roy. Soc. (London)* Ser. A. 170, 145, 165, 1939. *Cf. furthermore*\*).

mosphere reaches a minimum when the atmosphere is centrally symmetrical, i. e. as long as the central ion is placed freely with an undeformed atmosphere we have equilibrium in its micro-system.

*By deformation of the ionic atmosphere, the potential energy of the central ion is increased relative to the atmosphere, and — under the effect of the rising forces — the ion tends towards a new position with a new minimum of the potential energy; therefore, the central ion moves from a position with lower concentration of oppositely charged ions to a position with a higher concentration of these ions.*

*When the ionic atmosphere around two charged particles of like sign, ions or colloidal micelles, are brought to overlap due to Brownian movements of the particles, a new ionic atmosphere appears whose central particle is formed by the original particles which are driven towards one another under the re-establishment of equilibrium in the new system\*).*

Since the ionic atmosphere has a total charge of the same order of magnitude as the charge of the central ion, however of opposite sign, an ion with its atmosphere represents from outside an electrically neutral formation. Due to this electric shielding, two equally charged central ions can approach one

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\*) *Addendum:* Such a pair formation of central ions (or particles) might be regarded as an analogon to *Bjerrum's* ordinary association of oppositely charged ions. (*N. Bjerrum*, D. Kgl. Danske Vidensk. Selskab., Math.-fys. Medd. 7, 9, 1926 or *Ergebn. exakt. Naturwiss.* 6, 125, 1926.). It holds also for the new type of ion pairs that the free mobility of the ions is reduced. Component ions of an ion group may constantly be changing places with other free ions from the solution so that the "complete dissociation" is not invalidated (*N. A. McKenna*, *Theoretical electrochemistry*. Macmillan and Co. London 1939, p. 22.) The significance of the interdependence of ions of like charge for the general electrolyte theory, especially *Debye* and *Hückel's* theory, is obvious (*cf. S. Levine* and *G. P. Dube* (252)). In not very dilute solutions of colloidal dye-stuffs which are uni-multivalent electrolytes, aggregates consisting of ions of like sign were actually found (*G. Kortüm*, *Z. phys. Chem. B.* 33, 1, 1936. A general discussion on colloidal electrolytes, *Trans. Faraday Soc.* 31, 1—421, 1935.)

The ordinary view concerning the thickness of the double layer by definition *ad modum Debye-Hückel* might incite us to deny the possibility of these effects. However, calculations performed by *E. Güntelberg* lead to the following result. The contribution from the outer shells of the ionic atmosphere to the potential energy of the central ion is very considerable compared to the contribution of the inner shells. On this basis only, we understand the applicability of the *Debye-Hückel* theory which otherwise would be exposed to unperceptible special-phenomena in the immediate proximity of the central ion. (*E. Güntelberg*, *Kemisk Maanedssblad* 10, 151, 1929).

another without repulsion until the deformation of the ionic atmosphere begins. As a consequence of this now but partial shielding, a repulsion begins which, however, is much less than the *Coulomb* repulsion between central ions when they are deprived of their atmospheres. In the special case that the charges of the particles originate from a dissociation of molecules on the surface of the particles, the dissociation will be suppressed locally when the particles approach one another so that repulsion becomes less than when the charges were maintained.

If we imagine the interaction energy of the particles (attraction, repulsion) plotted in the usual way (with signs) as ordinates, and the distance between the particles as abscissae, we obtain a potential curve\*) which will generally show a minimum somewhere. If this minimum is not too deep and sufficiently close to the distance zero between the particles, the kinetic energy of the particles will be able to get over the minimum and to cause aggregation.

In *P. Debye* and *E. Hückel's* electrostatic electrolyte theory, 1923 (77, 78), (*E. Hückel*, 1924 (208), *W. Orthmann*, 1927 (313), *H. Falkenhagen*, 1932 (111), 1935 (112)), these authors try to explain the deviations of strong electrolyte solutions from ideal solutions by means of inter-ionic *Coulomb* forces. *Debye* and *Hückel* do not take into account a possible attraction between equally charged ions or a repulsion between oppositely charged ions. However, the preserving influence of the ionic forces upon the spherical symmetry of the ionic atmosphere appears in the relaxation force of this theory.

If a current be passed through an electrolyte, the ionic atmosphere round one or another arbitrary central ion will be deformed since the central ion moves in the direction of one electrode and the ions of the atmosphere move towards the other electrode. During this movement of the central ion, an atmosphere which is stationary relative to the central ion is formed by building-up in front of and break-down behind the central ion. Since the formation as well as the break-down of the ionic atmosphere lasts some time — the so-called time of relaxation — an asymmetry of the ionic atmosphere appears with an accumulation of charges of like sign in front of and charges of unlike sign behind the central ion. Due to this charge distribution, the central ion will suffer a retarding effect, independent of its own sign, *i. e.* the relaxation force. This force causes a reduced electric conductivity of the electrolyte solution. If the viscosity of the medium is increased, the reorganization of the ionic atmosphere requires more time (increase in time of relaxation), whereby the dissymmetry and the relaxation force of the atmosphere increase.

\*) *Addendum*: For the discussion of colloid-physical problems, potential curves have already been applied by *H. C. Hamaker* (209, p. 16).

In *P. Debye's* kinetic derivation (75) of the osmotic laws of strong electrolytes, he calculated finally the electric force acting upon an ion in an ionic solution the concentration of which varied in space.

It must be considered admissible that *Debye* and *Hückel* generally disregarded other ionic interactions apart from attraction between differently and repulsion between equally charged ions when dealing with dilute uni-univalent electrolytes. In the case of high-polyvalent electrolytes, however, this fact is of essential importance for the interpretation of a number of anomalies.

In the study of the most recent electrolyte literature, we find investigations by *J. G. Kirkwood*, 1936 (225), *I. Langmuir*, 1938 (243), and *S. Levine* and *G. P. Dube*, 1939 (252), which deal with these paradoxical interactions and which support the author's theory in all essential points.\*) The view that the electric double layer of colloidal particles might cause attraction instead of repulsion was pointed out for the first time by *A. W. Porter* and *J. J. Hedges*, 1922 (336).

Due to the enormous difference in size between an electrolyte ion and a multivalent colloid ion, a direct comparison is difficult, perhaps even inadmissible. It seems, however, as if the electrostatic cohesion pressure was playing a quite different part in colloidal systems, especially in the case of red blood corpuscles owing to their enormous electric charge and remarkable size.

*If we conceive the electrostatic cohesion pressure or rather the existing electric energy as producing condensation, and the kinetic energy of the Brownian movements as a dispersing factor which, however, promotes condensation by bringing the particles together and, thus, gives rise to rouleaux formation, we succeed in getting a concrete picture of the mechanism which makes a theoretico-physical treatment possible.\*\*)*

A few further remarks may, however, be added to the pre-

\*) *Addendum*: Cf. furthermore *A. J. Corkill* and *L. Rosenhead*, *Proc. Roy. Soc. (London)* Ser. A. 172, 410, 1939, who calculated exactly the partition of charges in a binary electrolyte between two planes and who found an attraction between the planes. The significance of the size of the particles for the stability of a dispersoid was treated by *H. C. Hamaker* (113, p. 186). *B. Derjaguin* (113, p. 203) should be mentioned as an opponent to the paradoxical ionic interaction.

\*\*) *Addendum*: With the mentioned simplified picture it is not prejudiced that other forces, e. g. *Van der Waal's* or *Kallmann - Willstätter's* forces (*Naturwiss.* 20, 152, 1932) are without any influence on the aggregation process, nor is it the author's intention to conclude from rouleaux formation to other haemagglutinations.

viously mentioned outline of the author's physical image of the aggregation process.

Since *Thomson's* theorem is a variational principle (for the minimum of potential energy) which is especially suited for the study of equilibria, the treatment of the total interaction between two given (colloidal) particles claims a more comprehensive variational principle from the dynamics of particles.

For the construction of the common ionic atmosphere of the particles, it seems furthermore necessary to replace the generally applied *Maxwell-Boltzmann* expression — which only holds in the case of statistical equilibrium — by a distribution function determined by a partial differential equation derived on the basis of the theory of the Brownian movements (*cf.* the calculation of the orientation of ellipsoids, § 37, *c.*, p. 128).

These very complicated investigations which are not yet terminated will be published later. If I, nevertheless, already beforehand venture to publish this theory in a popular formulation\*), this must be ascribed to my agreement with *Faraday's* view-point expressed in his correspondence with *Maxwell*, 1857 (*L. Campbell* and *W. Garnett*, 1884 (63)), to whom he writes

"There is one thing I would be glad to ask you. When a mathematician engaged in investigating physical actions and results has arrived at his conclusions, may they not be expressed in common language as fully, clearly, and definitely as in mathematical formulæ? If so, would it not be a great boon to such as I to express them so? — translating them out of their hieroglyphics, that we also might work upon them by experiment. I think it must be so, because I have always found that you could convey to me a perfectly clear idea of your conclusions, which, though they may give me the results neither above nor below the truth, and so clear in character that I can think and work from them. If this be possible, would it not be a good thing if mathematicians, working on these subjects, were to give us the results in this popular, useful, working state, as well as in that which is their own and proper to them?"

In the light of the mechanism described, the orientated aggregation of the corpuscles becomes comprehensible. In analogy to

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\*) Lecture given at the Danish Biological Society (*J. E. Thygesen* 1940, (416)).

electrostatics, we assume an ionic atmosphere with the greatest thickness where the geometrical curvature of the particle surface is greatest, *i. e.* at the edges of the disc shaped and at the points of rod shaped particles (*J. H. Jeans*, 1925 (211) ). The resulting form of the conglomerate should therefore be rouleaux and bundles, respectively; just this is what we observe. The well-known phenomenon, temporary deformation of erythrocytes to bell-shape, especially marked during a strong aggregation process — often a kind of “embrace reflex” — must be ascribed to the strong action of forces at the edges of the particles.

According to *E. Ponder* (333), the shape of the erythrocyte corresponds to an equipotential plane of a charged ring (*cf.* furthermore (334) ).

Finally, the electrolyte sensitivity of rouleaux formations may easily be explained by means of the proposed hypothesis and, furthermore, the remarkable decrease in aggregability with increasing electrolyte concentration and the significance of *Hofmeister's* ionic series for the stabilizing effect of electrolytes. As previously mentioned, *the aggregation forces increase with increasing thickness of the ionic atmosphere* just showing these features during a change in electrolyte concentration (*cf. H. Müller*, 1928 (287) ).

*The increase in erythrocyte aggregability by viscous substances* mentioned in § 8, p. 19 does not depend on the chemical constitution of the respective substances but *seems to follow the viscosity of the suspension medium*. On the basis of the above mentioned interdependence between the viscosity of the suspension fluid and the relaxation force which is only a special manifestation of the electrostatic cohesion pressure, the influence of viscosity upon rouleaux formation may also be explained by the author's new theory.



Section IV.  
THE AUTHOR'S EXPERIMENTAL  
INVESTIGATIONS.

A. AGGREGATION EXPERIMENTS.

§ 39. PERFORMANCE OF AGGREGATION EXPERIMENTS.

*a. Preparation of the blood sample.*

Blood was taken by means of vein puncture. In order to prevent clotting, 0.07 cc of a 20 per cent potassium oxalate solution was added to 5 cc blood, 0.11 cc was added to 8 cc blood. Blood was taken from fasting patients in order to avoid lipaemia. The sample was immediately divided in two portions, one of which was used for ordinary blood routine tests consisting of

- 1) per cent haemoglobin (*Haldane*),
- 2) erythrocyte count (millions/mm<sup>3</sup>),
- 3) colour index,
- 4) leucocytes per mm<sup>3</sup>,
- 5) sinking reaction in mm per hour.

By the separation of the blood sample in two parts, unnecessary traumatism of the blood corpuscles of portion II was avoided.

*The technique of the sedimentation test.*

The technique usually employed at the *Finsen Laboratory* was as follows. 0.2 cc physiological sodium chloride solution (0.9 per cent) and 1.8 cc oxalate blood obtained as described above were sucked up into a *Westergren's* 2 cc syringe. After careful mixing for one minute, the sample was sucked up to the uppermost mark of a *Westergren* tube (length 300 mm, diameter 2.5 mm) which was provided with a *Katz'* millimeter scale (220). The tube was placed vertically and kept standing for one hour at room temperature (20 °C). The time of reading was announced by an alarm-bell.

*Preparation of the test suspensions.*

From the well-mixed sample (II),  $\frac{1}{2}$  cc blood was filled into a micro test-tube containing a glass bead; from the rest of the blood sample, the erythrocytes were centrifuged off and the plasma was separated. Whole blood-plasma dilutions were not prepared until just before the start of the experiment. The amount of plasma, already measured in advance, was transferred into the micro test-tube and an exact amount of total blood from the carefully mixed blood sample was added by means of a capillary pipette; the content of the micro test-tube was then mixed a few times by means of the bead. As soon as the test-tube was brought in position, the stopwatch was started. In order to avoid currents in the suspension, blood and plasma were brought to thermal equilibrium in a water-thermostat.

In all experiments, except those in which the effect of shaking had to be investigated, the test-tube was at complete rest during the whole period of experiment.

*Taking of samples from the suspension*

occurred by means of a *Pasteur* pipette. At a given time, the mouth of the pipette was immersed to the middle of the test-tube and the sample was sucked up. In this way, the uppermost layer was avoided where an inhomogeneity appeared very rapidly due to sedimentation. A sucking up from the bottom of the test-tube would also produce falsifications due to accumulation of large aggregates.

The application of a pipette involves the risk that some of the corpuscles adhere to the wall of the glass tube, however, a too rapid transference into the counting chamber might split the aggregates.

*Filling of the counting chamber.*

Only slightly more than necessary for filling of the counting chamber (*Bürcker-Türk's* chamber, 0.1 mm high) was sucked up into the *Pasteur* pipette. After precise filling of the chamber, currents were never observed and, since photographing lasted only a short time, a possible evaporation had not to be taken into account. In this way, closing by means of vaseline could be avoided, which was of great advantage in series of experiments.

When currents appeared due to over-filling of the chamber, the results were markedly falsified, *i. e.* aggregation was found vastly increased relative to the preparations which were prepared *lege artis*.

*b. Photographic arrangement.*

An "Askania" film camera with accessories for microphotography was employed.

The illumination arrangement which was mounted on a photometer bench consisted of a light source and a filter. The lamp was mounted inside a lamp house with a movable lense and the light was filtered through a plano-parallel absorption cell, 5 cm thick, and filled with a 10 per cent copper sulfate solution. The cell served partly for the reduction of thermal radiation which might injure the preparation (*viz.* alter the corpuscle aggregation and cause currents), partly to obtain sufficient contrast between the red corpuscles and the diffusely grained, strongly illuminated suspension medium. After the cell, the light passed a rotating diaphragm which opened and closed for the light synchronously with the shutter mechanism of the film apparatus.

The light from the illumination device was directed towards a plane mirror of a Zeiss microscope, the iris diaphragm and condenser of which served for further regulation of the light. In order to attain the best possible contrasts in the picture, the condenser was slightly lowered so that the corpuscles were hit by convergent light. In this way, too strong and directly dazzling light through the suspension medium was avoided and excellent plastic pictures of the corpuscles were obtained. The contrast in the picture was improved by smaller diaphragms, however, the light intensity decreased simultaneously.

For the screening of the light in the observation room and in order to maintain a constant temperature around the preparation on the stage, the microscope was surrounded by a closed, electrically regulated thermostat (yet, most experiments were performed at room temperature).

The microscope was provided with a mechanical stage so that the preparation could easily be moved during counting *etc.*

In order to obtain satisfactorily sharp pictures, it was necessary to replace the ordinary eye-piece by a special photo-compensat-

ion ocular. Generally, the objective magnification was 10 times and that of the eye-piece 6 times. The microscope tube was lengthened by bellows and connected to the camera itself which was provided with an observation prism and an eye-piece so that the preparation could be observed during photographing every time it was illuminated for exposure. For practical reasons, the prism was always in use. When the illumination device and the microscope were adjusted, the exposure could be regulated by the sector diaphragm of the camera and the rate of exposure. The sharpness of the picture could be tested by means of a special arrangement on top of the camera; however, this was generally unnecessary, since the picture on the film was always sharp when the image in the eye-piece was sharp.

The rate of exposure could be regulated within a wide range, from 20 to 25 pictures per second until a few pictures per minute. This was done by means of a gear box and a resistance connected with the electromotor.

### *Photographing.*

Immediately after filling, the counting chamber was mounted on the microscope stage. Photographing began 1—2 minutes later when the corpuscles had sedimented; sharp pictures could not be obtained earlier. The time of measurement was generally defined as the time for filling of the chamber plus 1 minute.

The rate of sedimentation depended on the height of the haemocytometer and the size of the aggregates which again depended on the moment of taking a sample from the suspension.

Lacking a suitable "Schutzkolloid" (protection colloid) for complete cessation of erythrocyte aggregation, it was necessary to confine ourselves to the suppressing effect of sedimentation on the coagulation process. An attempt was made to avoid falsifications by rapid photography. When the pictures from various regions of the counting chamber were taken in the course of a few minutes, constant results could be obtained; in unfavourable cases (at relatively high concentrations and very unstable blood), the results were markedly falsified when photographing lasted too long, as aggregation continued, although slowly, in the chamber.

The more shallow the counting chamber, the fewer corpuscles occur per square at a given concentration, so that a great number

of pictures had to be taken to maintain a reasonable counting accuracy. Hence, a low chamber involved a long period of photographing, however, the risk of continued aggregation in the chamber was also reduced. Among the tested counting chambers

<i>Thoma-Zeiss</i>	height 0.05 mm
<i>Bürcker-Türck</i>	» 0.1 mm
<i>Fuchs-Rosenthal</i>	» 0.2 mm

the present author considers *Bürcker-Türck*'s chamber to be most practical for his special purpose.

In order to secure approximately the same counting accuracy, more squares of dilute than of concentrated suspensions were photographed. Owing to the application of a counting chamber instead of the ordinary slide-cover-glass preparations, photographs were obtained under the most uniform conditions. The time of exposure depended not only on the height of the counting chamber but primarily on the corpuscle concentration. During aggregation, the light absorption in the chamber preparation varied to some extent, since absorption (scattering) decreased with increasing aggregation.

In aggregation experiments, the photomicrographic film camera was especially suited for comfortable and rapid taking of single pictures of different squares of the respective preparation. (As regards the application to ordinary exposures, cf. § 41, p. 169). Agfa "Orthokine" of normal breadth (35 mm) was used for the negative film. Developing and copying were performed by the firm A/S Joh. Ankerstjerne, Copenhagen.

The negative was studied directly with a magnifying glass and also either by projection or by enlarging the copies of single pictures. Enlarged copies of the single squares and counting of the corpuscles on the enlargement was the easiest method, but rather expensive. Direct studies with a magnifying glass were tiring but could be carried out. The pictures were taken with so high a magnification (60 times) that single corpuscles of the rouleaux could directly be identified and counted on the enlarged copy with the naked eye (Fig. 4).

### c) Sources of error in the technique.

The most essential sources of error in the measurement of aggregation are the lack of protecting colloid and sedimentation.

Aggregation continued in the counting chamber, however, at a reduced rate as soon as the blood corpuscles sedimented. The influence of this phenomenon has been described previously (p. 157).

In very dilute suspensions used in aggregation experiments, rapid sedimentation (due to low viscosity) in the micro test-tube

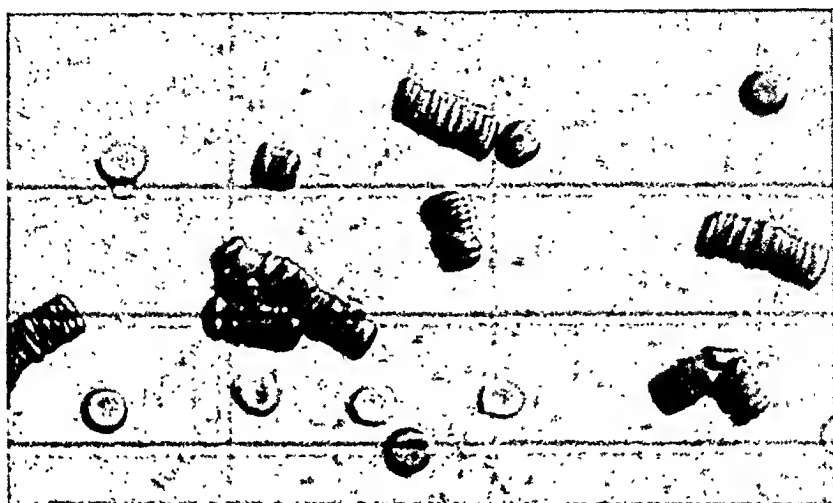


Fig. 4. "Rouleaux formation". Magnification 700 times; blood sample crt. No. 4.; erythrocyte count 3.80 Mil./mm<sup>3</sup>; sedimentation test 39 mm/1 hour (diffuse interface); blood-plasma dilution 1:50; temperature 20° C; time 300 sec.

is a serious source of error which is only partly eliminated by the above described taking of samples from the middle of the suspension. On account of the greater rate of sedimentation of larger aggregates relative to smaller aggregates, the measured time of coagulation becomes somewhat lower the later the sample was taken.

By counting the number of single and multiple particles and their multiplicity at a given time, the total number of single particles is calculated which is then considered the relative initial number. In this way, the influence of the decreasing number of particles — due to sedimentation — is equalized, but the disappearance of some of the large aggregates is not compensated completely.

A reader who is familiar with coagulation measurements on

colloids and dispersoids and who estimates the applicability of these measurements despite their considerable inaccuracy will hardly be discouraged by the above described difficulties in the case of blood corpuscle suspensions. Orientating results which are the only aim of the present investigations may easily be obtained. In studies to come, samples should be taken at the same time from different heights of the suspension, since the present estimations lead to a mean value, only. The question of a possible orthokinetic coagulation might thereby be elucidated (*cf.* the author's considerations, p. 168).

In order to attain a reasonable counting accuracy of the aggregation distribution, a suitable number of corpuscles must be counted. According to *P. Plum*, 1936 (331), the accuracy of ordinary erythrocyte countings in clinics does not depend on the area over which the corpuscles are distributed but mainly on the quantity really counted. *Hayem's* liquid applied to the dilution of blood annuls rouleaux formation. In aggregation experiments, rouleaux formation causes a very irregular distribution so that also the area is of some importance. In strong aggregation, a greater number of squares must be counted in order to secure the same accuracy as in a suspension with (the same concentration and) a slighter tendency to aggregation. In order to reach a given counting accuracy for conglomerates of a given multiplicity, it is necessary to count the more corpuscles the greater the size of the respective aggregate and the smaller the aggregation tendency of the blood investigated.

Counting a sufficient number of corpuscles will always enable us to reduce the counting error relative to the other faults of the method. In experiment A 1 (Table A 1c, *Appendix*, p. 201) the distribution of the various sizes of aggregates per square was determined and, moreover, the total number of aggregates of a given multiplicity; this experiment may give an idea of the counting accuracy.

#### § 40. RESULTS FROM AGGREGATION EXPERIMENTS.

*a. Characteristic distribution of aggregates; polydisperse coagulation; influence of the erythrocyte concentration upon aggregation.*

In order to illustrate the usual course of perikinetik coagulat-

ion in corpuscle-plasma suspensions we consider the result of an aggregation experiment. Experiment A 1, Table A 1a, first line (*Appendix* p. 200) shows the distribution of aggregates in a counting chamber preparation at a given time (600 sec).

If rouleaux formations appeared as conglomerates in a monodispersive system, *i. e.* supposing the same tendency to aggregation between micelles of arbitrary multiplicity, a number of double particles would primarily be formed and these would associate with single particles, thus forming triplet particles. Due to rather seldom collisions between double particles *inter se*, also quadruple particles would be formed, *etc.* (*cf. Smoluchowski's* coagulation theory, § 27, p. 67). As a measure of the aggregation ability of a suspension, the so-called time of coagulation is frequently used, *i. e.* the time that passes until the total number of particles ( $\sum v$ ) is half reduced. Employing *Smoluchowski's* notations (*cf.* p. 70), we get

$$\sum v = \frac{v_0}{1 + \frac{t}{T}}; \quad \text{for } t = T \text{ we have } \sum v = \frac{v_0}{2}. \quad (1)$$

If the number of unchanged single particles ( $v_1$ ) is regarded as an indicator of the course of coagulation, the time of coagulation may be defined as the time that passes until the number of single particles is reduced to  $\frac{1}{4}$ .

$$v_1 = \left[ \frac{v_0}{1 + \frac{t}{T}} \right]^2; \quad \text{for } t = T \text{ we have } v_1 = \frac{v_0}{4}. \quad (2)$$

By means of *Smoluchowski's* other formulas for the different numbers of particles or their combinations, the time of coagulation may, furthermore, be calculated in various ways. These times of coagulation agree only in the case of monodispersive coagulation, while in other cases with deviating courses of coagulation, the time of coagulation must be interpreted as arbitrarily calculated. The arbitrarily calculated time of coagulation may serve as an expression of the course of a coagulation process which is not founded on given formulas. One and the same time of coagulation may, however, correspond to numerous different courses of coagulation which are only unambiguously



given by the distribution of particles of a given size at different times.

By means of the expression

$$\frac{R}{r} = \frac{3\eta}{2k\Theta\nu_0 T} \quad (3)$$

( $\eta = 0.02$  Poise (plasma),  $\Theta = 293^\circ$  Kelvin, experiment at  $20^\circ\text{C}$ ), and by substitution of the applied formula for  $T$ , viz.

$$T = \frac{t \sum \nu}{\nu_0 - \sum \nu}, \quad (4)$$

*Smoluchowski's* ratio between action radius and particle radius may be calculated and this magnitude may be employed for an analysis of the studied coagulation process.

In comparison with the suspension investigated in experiment A 1, the second line of Table A 1a (*Appendix* p. 200) shows the particle distribution at (rapid) monodispersive coagulation. The *Smoluchowski* distribution in the imaginary comparative suspension — which is assumed to be of the same concentration as the suspension of the experiment — was calculated for the moment when the number of single particles corresponds to that of the test suspension.

In the test suspension,  $T$  was determined (arbitrarily) from

$$T = \frac{t}{\sqrt{\frac{\nu_0}{\nu_1}} - 1}. \quad (5)$$

In the imaginary comparative suspension,  $T$  was calculated from

$$T = \frac{3\eta}{2k\Theta(R/r)\nu_0} \quad \text{with} \quad \frac{R}{r} = 2, \quad (6)$$

and the moment when  $\nu_1$  has the same value as in the test suspension was evaluated from

$$t = \left( \sqrt{\frac{\nu_0}{\nu_1}} - 1 \right) T. \quad (7)$$

The number of aggregates with different multiplicity was calculated from

$$\nu_k = \frac{\left(\frac{t}{T}\right)^{k-1}}{\left(1 + \frac{t}{T}\right)^{k+1}} \nu_0. \quad (8)$$

When comparing these two lines of Table A 1a, the difference becomes evident. While the number of multiple aggregates of the *Smoluchowski* distribution decreases vastly with the multiplicity, the blood corpuscle experiment reveals a tendency to form an equal amount of multiple conglomerates. Consequently, it is proved that (the rather advanced) rouleaux formation does not occur as a coagulation in a monodispersive system — as originally assumed by *E. Ponder* (333) who was the first to carry out counting aggregation experiments on erythrocyte suspensions.

The tendency of the aggregates to obtain an approximately uniform size may explain a phenomenon which is well-known from the usual technique of sedimentation tests, *viz.* that the corpuscle column generally sinks with a sharp boundary. When the erythrocytes show different tendencies to aggregation, rapid sinking leads to an indefinite diffuse interface (*cf.* § 4, p. 12 and § 18, p. 40).

If the time of coagulation of the suspension is calculated as described above from  $\nu_0$  and  $\nu_1$ , we get  $T = 980$  sec. In order to obtain the same reduction of the number of single particles in a monodispersive coagulation  $\left(\frac{R}{r} = 2\right)$ , the time of coagulation must be c. 7 times greater; this means that samples should be taken 4514 sec, instead of the applied 600 sec, after the beginning of the experiment. First after 4.5  $T$  or 4.5 · 7370 sec, the maximum number of 8 tenfold particles would have been formed (formula 27, § 27, p. 70), while the suspension of the present experiment contained 11 particles of this type after 600 sec.

Hence, coagulation of the present suspension occurs much more rapidly and intensely than the *Smoluchowski* coagulation. We are concerned with a so-called polydispersive coagulation, since already formed conglomerates act as nuclei of coagulation for smaller compound particles, especially for single particles.

The correctness of this interpretation appears from the following measurements. Table A 2a (*Appendix*, p. 201) shows countings carried out after 5, 7, and 10 minutes on samples from the same

blood dilution. The ratio  $\frac{R}{r}$  increases with time (for calculation, *cf.* above) due to the increasing polydispersity which promotes coagulation (Table A 2b, *Appendix* p. 202). The countings indicate the same characteristic distribution of the micelle multiplicity as previously discussed. Table A 3 (*Appendix*, p. 202) contains the results from three different dilutions of the same blood where the samples were taken at the same time. Also the decreasing  $\frac{R}{r}$  with decreasing concentration shows the influence of the polydispersity.

In the case of ordinary colloids, a difference between polydisperse and monodisperse coagulation can only be proved when the ratio of the radii of large and small particles amounts to at least 10. If the ratio is less, polydisperse coagulation cannot be differentiated from monodisperse coagulation. In the case of erythrocytes, however, both aggregation experiments and the direct study of rouleaux formation under the microscope reveal that multiple aggregates — even two- and threefold conglomerates — more easily associate with single particles than the latter aggregates mutually.

Hence, monodisperse coagulation occurs only in the very beginning of the process, *viz.* before the formation of considerable amounts of two- or threefold conglomerates; however, satisfactory measurements are rather difficult to perform at that time because of the lack of a protecting colloid.

As a promoting factor of polydisperse coagulation, the growth of erythrocyte aggregates to longer and longer rods must be emphasized.

Direct observation of rouleaux formation under the microscope (and still clearer slow films which will be described later, § 41, p. 170) indicate that attractive forces act between erythrocytes. On account of intercorpuscular forces, the coagulation probability for conglomerates of unequal size becomes greater than is expected in view of the geometrical shape of the particles (*cf.* H. Müller, 1928 (287, p. 260)). The effect of smaller compound-aggregates as nuclei of coagulation must be considered an indirect proof of the existence of such forces; in any case, rapid coagulation of blood corpuscle suspensions cannot be produced by Brownian movements and polydispersity, only.

The calculation carried out previously in connection with experiment A 1 (*Appendix*, p. 200) showed a course of coagulation where only Brownian movements were effective. § 33, p. 97, contains the author's analysis of the influence of intercorpuscular forces upon monodispersive coagulation. The mathematical treatment of the still unsolved problem of coagulation in arbitrary polydispersive systems was initiated by *H. Müller* (288).

Since the present discussion until now dealt with rapidly aggregating blood corpuscle suspensions, it is obvious that "rapid" coagulation was involved, *i. e.* coagulation in which every collision between particles leads to aggregation. In suspensions with a very slight aggregation tendency we may certainly speak of "slow" coagulation, since direct microscopical observation proved that only a certain fraction of the collisions resulted in aggregation (*cf.* § 27, p. 72). Also in these cases (experiments A 8 and A 9, Table A 4, *Appendix*, p. 202), coagulation occurs polydispersively. According to *H. Müller* (287), the effectiveness of the collisions (fraction  $\epsilon$ ) increases with increasing size of the particles whereby the course of coagulation becomes "autocatalytic". It must be assumed that the transition from rapid to slow polydispersive coagulation is rather vague.

#### *b. Relation between sinking reaction and aggregation.*

In order to illustrate the well-known symbasy between sinking reaction and erythrocyte aggregation (§ 4, p. 10), some aggregation experiments were carried out on blood samples with varying sinking reactions. Almost the same corpuscle concentration was employed in all cases and the samples used for countings were taken at the same time (5 and 10 min.) after the start of the experiment. A number of measurements of this kind are comprised in Table A 5a (*Appendix*, p. 203). The table reveals that  $\frac{R}{r}$  which is inversely proportional to the time of coagulation  $T$  increases with increasing sinking reactions at both the chosen instances.

A comparison of the samples taken after 5 min. showed that the degree of polydispersity so essential for the course of coagulation appeared earliest and most intensely in samples with a high sinking reaction, thus indicating the participation of inter-

corpuscular forces. The samples taken after 10 min. showed the greater acceleration and aggregation, the more pronounced the degree of polydispersity at the early time (Tables A 5b and A 5c, *Appendix*, pp. 203 and 204). Also direct microscopic investigation of the suspensions proved that intercorpuscular forces were the stronger, the more instable the suspensions.

*c. Temperature dependence of the aggregation.*

For the investigation of the influence of temperature upon aggregation, samples of the same concentration and from the same time were compared at different temperatures (*cf.* Table A 6, *Appendix*, p. 204).

The tendency to aggregation seems to increase slowly with decreasing temperature. In one single case (sample crt. No. 1, *Appendix*, p. 198), this occurred so rapidly that the presence of cold-agglutinin must be assumed. Further attempts to prove the presence and to explain the effect of cold-agglutinin have not been made, despite the fact that later studies must pay due regard to this phenomenon\*). At the highest temperatures, a possible thermo-stabilization must certainly also be kept in mind.

The general observation of increased rouleaux formation with increasing temperature may possibly be ascribed to slightly heated preparations where currents in the liquid have an accelerating effect (*cf.* below, § 40, c., p. 167). *E. Ponder's* experiments (333) are very difficult to interpret, since shaking played a part to which rouleaux formation is apparently not indifferent. The conductivity measurements at different temperatures, described in § 43, p. 189, showed a decreasing steepness of the tangent in the origin of the conductivity curve with increasing temperature. This result indicates a decreasing rate of rouleaux formation.

*d. The effect of emulsoids upon aggregation. The sinking reaction curve of tylose blood.*

The aggregation promoting effect of certain emulsoids was investigated only in one case, *viz.* tylose (methyl cellulose), and even this case was studied half quantitatively. The degree of aggregation increased with increasing concentration of tylose (*cf.* Table A 7, *Appendix*, p. 205). In almost plasma-free suspensions,

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\*) *Cf.* footnote p. 12.

tylose could replace the plasma proteins. The direct microscopic investigation showed beautiful disc shaped erythrocytes and regular rouleaux formation. The number of various sizes of aggregates in suspensions containing tylose was distributed in the same way as in ordinary blood corpuscle-plasma suspensions.

Corresponding to the increased aggregation, tylose produced a higher rate of sedimentation despite the increased viscosity of the dispersion fluid. Table A 8 (*Appendix*, p. 205) contains the sinking reaction of blood before and after addition of tylose. The following mixtures with oxalate blood (crt. No. 5, *cf.* p. 198) were used.

- I. Undilute oxalate blood;
- II. 5 cc blood+1 cc isotonic glucose solution;
- III. 5 cc blood+1 cc isotonic glucose solution with 0.5 per cent tylose;
- IV. 5 cc blood+2 cc isotonic glucose solution;
- V. 5 cc blood+2 cc isotonic glucose solution with 0.5 per cent tylose.

Figure A 1 (*Appendix*, p. 206) shows the curve of the sinking reaction of preparations III and V. As usually, the sinking reaction is plotted in mm as axis of ordinates, and the time in minutes as axis of abscissae. The time of aggregation determined by extrapolation as described in § 19 (p. 46) amounted to 17 and 11 minutes, respectively. All values were measured at room temperature.

The shape of the sinking reaction curve of tylose blood corresponds exactly to that of ordinary blood (*cf.* § 19, p. 45). Relative to the corresponding control mixture (in order to attain the same erythrocyte concentration and the same dilution of the plasma proteins), we obtain a shorter time of aggregation after addition of tylose, thus indicating a more rapid rouleaux formation. The steepness of the linear part of the curve in the case of tylose blood sedimentation exhibits the high degree of aggregation.

*e. The influence of shaking upon aggregation.*

The influence of shaking on the aggregation process was demonstrated in one single quantitative and numerous half quantitative experiments. After very slight shaking or rocking (to and

fro twice per min), aggregation was markedly increased relative to the aggregation of the standing control suspension (Tables A 9a and A 9b, *Appendix*, p. 207). The weak currents in the liquid increased aggregation considerably, as is well-known from the work with counting chambers where they have a disagreeable effect. Half quantitative experiments proved that rapid shaking reduces or checks rouleaux formation; this occurred primarily by a disintegration of large conglomerates.

On account of the influence of shaking and currents on aggregation, *E. Ponder's* slight shaking of the test suspension (*cf.* pp. 88 and 191) must be abandoned, as previously mentioned; presumably, it was his intention to avoid sedimentation.

#### *f. Completing remarks.*

In the above described investigations of aggregation, only perikinetik coagulation is taken into account. The question of whether orthokinetic coagulation is possible in blood samples during the sedimentation test may be discussed briefly.

Since a certain degree of polydispersity is a condition of orthokinetic coagulation, the latter cannot appear in the very beginning of aggregation. The aggregation which becomes more and more polydispersive occurs with so great an intensity that single particles disappear rapidly and, hence, orthokinetic coagulation cannot take place in this phase of the aggregation process. The large conglomerates of rather uniform size subsequently continue coagulating according to *Smoluchowski's* theory until hydrodynamic conditions, *viz.* currents due to sedimentation, limit the final size of the aggregates. Since the appearance of orthokinetic coagulation requires certain relations between the size of the aggregates, also the last phases of the blood sedimentation process offer only slight possibilities for this type of coagulation.

In contradistinction to *H. Gessner's* interpretation, 1931 (151), "Die Fallkurven nehmen alsdann eine S-förmige Gestalt an und die Form der Kurven lässt mit Sicherheit auf eine durch orthokinetic Koagulation beeinflusste Sedimentation schliessen", the shape of the sinking curve may in a natural way be explained on the basis of the discussed considerations. During polydispersive coagulation represented in the first bend of the curve (aggregation phase), orthokinetic coagulation is improbable. In the

sedimentation phase, the linear course of the sinking reaction curve indicates that the final size of the conglomerates is reached. The last bend of the curve must be ascribed to a packing effect which can only be avoided in *Swedin's* modification of the apparatus (*cf.* § 19, p. 48).

## B. KINEMATOGRAPHY.

### § 41. DIRECT MEASUREMENT OF INTERCORPUSCULAR FORCES.

While coagulation processes are generally studied quantitatively by the measurement of the "rate of coagulation" which is an expression of the total course of the process, only, the determination of intercorpuseular forces, the motive power of the coagulation mechanism itself, might offer a new basis of research of the aggregation phenomena.

Since the so-called "radius of action" of *Smoluchowski's* mathematical coagulation theory (§ 27, p. 68) seems to represent a — though very simplified — picture of coagulation forces, the author has made an attempt to generalize this theory (§ 33, p. 97).

The expression found for  $R$  (*cf.* formula 25, p. 102) contains the potential energy of the coagulating particle (position energy) relative to the nucleus of coagulation, *i. e.* the work which has to be performed or may be gained in order to approach the coagulating particle to the nucleus of coagulation. Since we only know the effect of Brownian movements on the particles in the form of their kinetic energy, it seems most reasonable to express the intercorpuseular forces by the energy introduced into the system. If this energy is smaller than that of the Brownian movements, the system will disperse, in the opposite case it will coagulate. When the magnitude of forces and their distance dependence are known, the coagulation work (and thereby the radius of action) may be calculated by quadrature.

A direct method of determination of intercorpuseular forces could only be developed in systems where the forces act beyond the immediate proximity of the particles. The theoretical basis has been discussed previously (*cf.* § 34, p. 105) in the present



paper. The correction for the increased resistance to the particle movement between plano-parallel walls was also discussed (cf. § 21, p. 53).

As the method requires some knowledge of the particle displacement during small time intervals, an attempt was made to take motion pictures of the aggregation process. The apparatus and accessories are described in § 39, b., p. 156.

The microscope magnification was 120 times and 240 times (objective 20 times and compensation ocular 6 times and 12 times). The velocity of filming was 36 pictures per minute. The dilution of corpuscle-plasma suspensions was about 1 : 200. In order to avoid too rapid sedimentation, *Fuchs-Rosenthal's* haemocytometer was employed which is 0.2 mm high.

During filming of the movement of a given pair of particles, the microscope adjustment had to be corrected continuously due to sedimentation of the erythrocytes. Frequently, one of the particles disappeared from the field of vision because of its greater or smaller rate of falling relative to the other particle. Therefore, it was necessary to give up filming one single pair of particles and instead to apply a lower magnification (120 times) and a greater field of vision.

For a detailed study of the films served a projection apparatus with automatic stop as well as forth and reverse gear. By means of this apparatus, it became possible during observation of the film to choose and to observe different pairs of particles. When an aggregating pair was found, the film was inspected step by step and the distance between the centres of the particles was measured on the screen.

In spite of numerous experiments, it has not been possible — due to sedimentation — to find pairs of particles which remained only approximately within the plane of the picture so that reasonable measurements could be obtained. The previously given formulas furthermore claim that the spatial position of the centre-line, *i. e.* the line joining two centres, is known. Experiments with stereoscopic pictures could, however, not be performed.

The films proved to be an excellent supplement to direct observations in the microscope. To render direct observation possible, the rate of motion of the erythrocytes must exceed a given value. Owing to the considerable acceleration of the pro-

cess on the film (reproduction speed 20—25 pictures per sec, while filming speed 0.6 pictures per sec), also very slow phases of the movements became clearly visible.

A film of rouleaux formation and an example of isoagglutination (A-corpuscles in B-serum) were presented during a lecture given in the Biological Society, Copenhagen (*J. E. Thygesen*, 1940 (416) ).

### C. CONDUCTIVITY MEASUREMENTS.

#### § 42. EXPERIMENTAL TECHNIQUE.

##### *a. Conductivity cells, motor, thermostat, and chronograph.*

##### *Conductivity cells.*

The construction of a suitable cell for the investigation of conductivity phenomena involved some technical difficulties. The movement of the blood for disaggregation of rouleaux formations could be produced by streaming, shaking (rocking), or stirring.

Since streaming required rather large amounts of blood, it was attempted to keep a small amount of blood flowing to and fro between two containers where the air was alternately rarefied and compressed over the liquid surface. The pump consisted of a ring of an open glass tube which by means of a large stopper was fastened to the horizontal axis of a car's screen wiper. From the upper ends of the glass ring which was half filled with mercury, rubber tubings led to the blood containers.

Even at rapid streaming, the measuring instrument showed small deflections when the blood was allowed to stand for a moment, every time the direction of streaming was changed. *H. Fricke* and *S. Morse*, 1926 (134), employed a cell with combined streaming and shaking. Because of the immediate start of the aggregation process and the conductivity phenomenon, a continuous movement of the liquid was necessary.

Variations in the resistance capacity of the cell appeared during rocking which was to some extent applicable in preliminary experiments, while shaking was completely impossible due to foam formation. The surface active substance octyl alcohol could not be applied, since this might cause a change of surface of the erythrocytes and the electrodes.

The generator which was built according to the heterodyne principle could be adjusted to frequencies between 10 and 20 000 cycles.

In one of the two circuits coupled to the generator (cf. Fig. 6), the phase could be continuously altered by means of a phase variator and the amplitude could be regulated by means of a

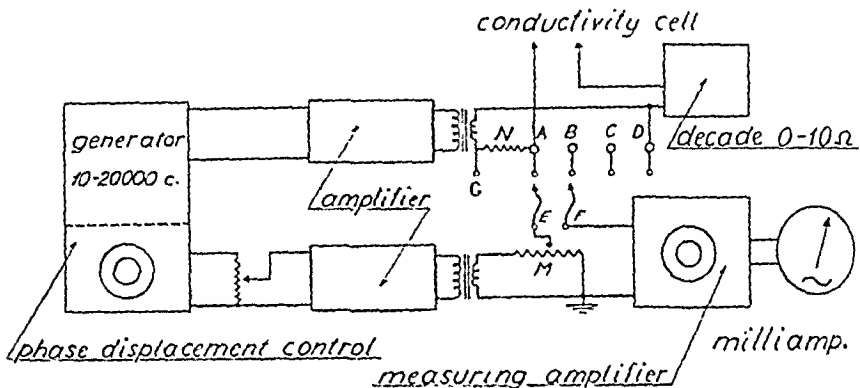


Fig. 6. Heterodyne compensator for the measurement of the blood impedance. (For explanation, cf. the text).

potentiometer with coarse and fine adjustment. The two alternating voltages had the same frequency but not necessarily the same amplitude. Both circuits contained valve amplifiers with low frequency output transformers. The secondary windings of the low frequency transformers entered the bridge circuits I and II.

The conductivity cell was connected in series with the clamps A and D of a decade rheostat of circuit I (the clamps B and C were not in use). By means of a shift gear, standard resistances (N) of 30, 100, 300, 1000, and 3000 ohms could be inserted. The potentiometer resistance (M) of circuit II was constant.

The zero instrument of the compensation arrangement was an a. c.-milliamperemeter (d. c.-milliamperemeter with copper oxide rectifier), the current being amplified in a measuring amplifier with adjustable amplification power (output control); low amplification at coarse adjustment and full amplification at fine adjustment and during measuring.

One lead to the measuring amplifier was connected to zero of the resistance ( $M$ ) of the measuring potentiometer, the other lead to the point  $F$  of a switchboard. The second terminal  $E$  of the switchboard represented a movable point on the measuring resistance, *i. e.* a variable part of which could be put in series with the zero instrument.

Between  $E$  and  $F$  of the shift gear different impedances of circuit I could be inserted. However, only the following two connections were used

- 1)  $G-E$  and  $A-F$
- 2)  $A-E$  and  $D-F$ .

As sources of e.m.f. in the measuring circuit appears the fall of potential across the two inserted impedances (I. standard resistance or conductivity cell+decade rheostat, II. the inserted part of the measuring resistance). When these two potential drops are equal in magnitude and phase, the milliamperemeter will not show any deflection.

#### *Application of the measuring apparatus.*

After having checked the zero point of the scale, the desired frequency is adjusted on the frequency scale of the generator.

The conductivity cell and the decade rheostat are switched in series with circuit I; the resistance of the decade rheostat is eliminated; the suspension is stirred with a speed which guarantees full dispersion and hence constant resistance. Subsequently, one of the standard resistances is inserted into the measuring circuit, the potentiometer is adjusted to 100, and the potentiometer and the phase shift are adjusted until the milliamperemeter shows a minimum (on account of "noise", the milliamperemeter will always indicate a minute current). Each of the potentiometer divisions represents 1/100 of the inserted standard resistance (at an adjustment to 50, each division represents 1/50, *etc.*). The potentiometer remains untouched and a movable needle of the phase variator is adjusted to zero.

Finally, the unknown impedance of the conductivity cell is introduced into the circuit, the potentiometer and the phase variator are adjusted again until the instrument shows a minimum current. The measuring potentiometer now shows the required

impedance (in ohms) and the phase variator indicates the phase shift (in degrees). When a standard resistance of a wrong order of magnitude has been chosen, another one is inserted, *etc.*

When the impedance of the fully dispersed suspension is found, the adjustment of the apparatus is left unchanged and stirring is ceased. The moment when given values are attained on the scale of the milliamperemeter is registered, *i. e.* half or whole divisions are determined by means of the chronograph or a stopwatch.

After a certain time of stirring, when the impedance has reached the initial value, the experiment be repeated.

The deflection of the zero instrument indicating the deviation from balance of the measuring arrangement is standardized in every experiment by means of the decade rheostat in series with the conductivity cell. During stirring of the suspension and after the circuit is brought to balance, 1, 2, - - - - 10 ohms are switched in, and the deflections of the milliamperemeter are read. Plotting these values in a coordinate system leads to a standardization curve of every experiment. From this curve, the increase in resistance above the initial value is determined.

The "Wirkwiderstand" (effective resistance) is, as well-known,

$$W = Z \cos \phi \quad (9)$$

where  $Z$  is the impedance,  $W$  the ohmic resistance, and  $\phi$  the phase angle. Due to the very small phase angles (about  $+1^\circ$  at 2000 cycles) in all experiments, the measured impedances are regarded as pure ohmic resistances; in any case, the correction would be without any importance for the present purpose. From the resistance  $W$ , the specific conductivity  $\kappa$  is calculated in the usual way by means of the formula

$$\kappa = \frac{1}{W} C, \quad (10)$$

where  $C$  is the cell constant or resistance capacity of the conductivity cell.

If the conductivity effect is so great that the scale of the milliamperemeter does not suffice — what may happen sometimes even in short-lasting experiments and frequently in long-lasting experiments — the change in resistance is measured by a variat-

ion of the measuring potentiometer until the zero instrument shows a current minimum. In this case, the change in resistance cannot be read directly from the potentiometer but, if the standard resistance and the resistance of the blood are of the same order of magnitude, it becomes almost twice the value read at the instrument. This holds under the supposition that the potential across circuit I is not changed due to resistance increase. With the small variations of resistance in the case of blood, this supposition can be considered fulfilled.

The standard resistance be denoted as  $N$ , the resistance of the fully dispersed suspension as  $B$ , the increase in resistance of the effect as  $F$ , and the readings of impedance before and after the occurrence of  $F$  be denoted as  $Z_0$  and  $Z_1$ , we get

$$F = \frac{(Z_1 - Z_0) B (N + B)}{Z_0 (N + B) - Z_1 B}. \quad (11)$$

If  $i_2$  is the current in circuit II,  $E_B$  and  $E_{BF}$  the potential differences across  $B$  and  $B + F$  of circuit I, respectively, where  $E$  is the potential across the whole circuit, we obtain

$$E_B = \frac{B}{N + B} E = Z_0 i_2 \quad \text{and} \quad E_{BF} = \frac{B + F}{N + B + F} E = Z_1 i_2. \quad (12)$$

By division, the unknown  $i_2$  is cancelled, and we find

$$\frac{Z_0}{Z_1} = \frac{B}{N + B} \cdot \frac{N + B + F}{B + F} = \frac{B(N + B) + BF}{B(N + B) + (N + B)F}. \quad (13)$$

A solution of the equation with respect to  $F$  leads to the above formula for  $F$ .

In order to illustrate the course of a conductivity measurement, an example of the report is presented below which, of course, is more detailed than the tables given in the *Appendix*.

12—10—39. Experiment No. *K* 2 (*Appendix*, p. 209).

Conductivity cell II ( $\log C = 0.17371$ ).

Oxalate blood sample crt. No. 15.

Temperature  $24^\circ.90$  C.

Frequency 2000 cycles.

Standard resistance  $N = 300$  ohms.

Measuring potentiometer  $Z = \text{scale value } 100$ .

Phase angle  $\phi = 0$ .

At the fully dispersed suspension, the initial value of the impedance  $Z = 59.1$  divisions or  $59.1 \cdot \frac{300}{100} = 177.3$  ohms. ( $\phi = 1.0$ ).

Scale divisions of the milli- amperemeter	Total impedance in ohms	Specific con- ductivity in ohm <sup>-1</sup> cm <sup>-1</sup>	Time in seconds
0	$177.3 + 0.00 = 177.30$	8.414	0
1	$177.3 + 1.25 = 178.55$	8.355	2
2	$177.3 + 2.10 = 179.40$	8.316	3
3	$177.3 + 3.10 = 180.40$	8.269	7
4	$177.3 + 4.05 = 181.35$	8.226	14
5	$177.3 + 5.02 = 182.32$	8.182	23
6	$177.3 + 6.00 = 183.30$	8.139	37
7	$177.3 + 6.95 = 184.25$	8.097	61
8	$177.3 + 7.95 = 185.25$	8.053	97
9	$177.3 + 8.92 = 186.22$	8.011	143
10	$177.3 + 9.92 = 187.22$	7.968	194
$Z = 63.0$	$177.3 + 19.37 = 196.67$	7.585	240

The increase in impedance corresponding to every division of the scale of the milliamperemeter is read on the standardization curve which is a straight line obtained by graphic evaluation of the following values.

Decade rheostat, ohms	1	2	3	4	5	6	7	8	9
Milliamperem., scale	0.8	1.8	2.8	3.9	5.0	6.0	7.05	8.1	9.1

For the increase in impedance at the time 240 sec., which is beyond the range of the zero instrument, the formula for  $F$  was applied:

$$\begin{aligned}
 N &= 300; & B &= 177.3; & N+B &= 477.3; \\
 Z_0 &= 59.1 \cdot 3 = 177.3; & Z_1 &= 63.0 \cdot 3 = 189.0; \\
 F &= 19.37.
 \end{aligned}$$

#### *Accuracy of the measurements.*

The scale of the measuring potentiometer permits readings of one tenth of a division, *i. e.* 0.3 ohm at a standard resistance of 300 ohms and  $Z = 100$  ( $\phi = 0$ ), 0.2 ohm at  $N = 100$  and

$Z = 50$  ( $\phi = 0$ ), hence an accuracy of 0.1 and 0.2 per cent, respectively. The sensitivity of the zero instrument which depends on the magnitude of the measured impedances is on average 0.9 ohm per division at impedances of about 200 ohms. It was easy to read  $1/20$  of a division, corresponding to 0.045 ohm, *i. e.* an accuracy of 0.02 per cent.\*)

On account of this accuracy the initial impedance is given with one, the increase in impedance with two, and the specific conductivity with three decimals. The poor accuracy of the initial impedance is of minor significance for the author's experiments, since we are mainly interested in relative values.

*c. Performance of an ordinary conductivity experiment.*

When full disaggregation of "rouleaux formations" is obtained by stirring of the blood at a suitable rate, and the electrical conductivity of the blood is measured at various times after cessation of the stirring, a coagulation experiment is performed.

The normal determination of the conductivity effect was carried out in this way. Only when stirring at or above a certain speed, full disaggregation could be obtained, as was detected by a maximum conductivity effect. A still higher rate of stirring than the critical speed should be avoided because the corpuscles may easily haemolyse due to injuries. Every conductivity experiment was repeated a few times. The accurate adjustment of the conductivity of the fully dispersed suspension was of greatest importance, since small deviations could cause a falsification of the effect.

In order to avoid thermostabilization, only fresh blood samples were used for the experiment. Blood with haemolysis was unsuitable. As anti-coagulants, 0.07 cc of a 20 per cent potassium oxalate solution per 5 cc of blood was used in all cases.

The blood sample was cooled down to room temperature and was moved slightly in a flat glass dish for about 10 min in order to obtain equilibrium with the atmosphere. After filling of the conductivity cell the latter was immediately and completely closed.

On a minor portion of the sample, a general blood test was per-

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\*) *Addendum*: A detailed discussion of the accuracy of impedance and phase angle measurements was given by M. Trier and E. Warburg, D. Kgl. Danske Vidensk. Selskab., Math.-fys. Medd. 18, No. 10, 1941.



formed to the same degree as in the aggregation experiments (*cf.* § 39, a., p. 154). With respect to various calculations, a determination of the volume per cent of the erythrocytes would have been desirable, however, the erythrocyte number may give some information, since 5 Mill. erythrocytes per cc correspond to 43 volume per cent in the case of non-anaemic blood (*cf.* § 6, p. 15).

To facilitate a comparison of conductivity curves, the measurements were converted into changes of the specific conductivity (denoted as  $\Delta\kappa$  in the tables of the *Appendix*) by subtracting the initial values of conductivity from the measured values, so that the curves obtained a common origin. The changes in conductivity expressed as  $\text{ohm}^{-1}\text{cm}^{-1}$  are plotted as axis of ordinates and time in sec as axis of abscissae. It was considered preferable to compare the changes in conductivity directly without conversion into per cent of the conductivity of the fully dispersed suspension, since the effect depends only indirectly on this magnitude through the volume concentration of the erythrocytes and the conductivity of the plasma.

### § 43. RESULTS OF CONDUCTIVITY EXPERIMENTS.

*a. The typical curve of the conductivity effect. The influence of the position of the electrodes. The conductivity phenomenon's independence of the sedimentation.*

When comparing the conductivity curves of different blood samples (*cf.* Figs. A 3, A 4, A 5, pp. 210-212), a steeply decreasing first part was found as a common characteristic; this steep part was followed by a weakly decreasing second region. When the experiments last sufficiently long, a third region might be added which, however, will not be considered belonging to the real conductivity effect. Concerning the observation of the so-called "paradoxical conductivity effect", *cf.* below § 43 h., p. 189.

In some preliminary experiments in which the sample was shaken (rocked) instead of stirred, the conductivity phenomenon was found to be independent of the placement of the electrodes, *i. e.* the effect was independent of corpuscle sedimentation. This was, however, not the case with the third region of the conductivity curve.

When the electrodes were placed as in the permanent arrangement (*cf.* Fig. 5, p. 175), the conductivity curve decreased again more rapidly after having passed an inflection point which, as may easily be shown, represents the time of aggregation of the erythrocytes (*cf.* § 19, p. 46 and § 40, p. 167). The increase in resistance after the point of inflection is only an expression for the packing of the blood corpuscles above the lower electrode. When both electrodes were placed upwards, the third region of the curve showed a decrease in resistance due to a decrease in concentration of the corpuscles by sedimentation. In experiment *K 2* (*Appendix*, p. 211) in which very rapidly sedimenting blood has been used, the effect of sedimentation on the conductivity may already be noticed after the lapse of 3 minutes (*cf.* Fig. A 2, *Appendix*, p. 209). A time of agglomeration of c. 3 min. in the case of blood with a sinking reaction of 137 mm/h is in good agreement with our experience concerning the shape of the sinking reaction curve.

Since the conductivity phenomenon is the object of the present investigations, the duration of most experiments was below the time of agglomeration of the respective blood sample. Also for practical reasons, *e. g.* with respect to the constancy of the sensitive and complicated apparatus, it was rather difficult to extend the experiment over the time of agglomeration, especially in the case of samples with a low sedimentation rate.

Since the greatest part of the conductivity effect, *viz.* the steeply decreasing first part of the curve, occurs within a rather short time of 15–60 seconds (experiment *K 2*,  $0.275 \text{ ohm}^{-1} \text{ cm}^{-1}$  or more than half the effect in the course of 37 sec.), also this fact excludes sedimentation as a cause of the conductivity effect. This result is in agreement with *B. Swedin's* experiment, 1936 (407), in *H. Theorell's* cataphoresis apparatus described in § 19, p. 46.

*b. The influence of a.c.-amplitude and frequency. The phase shift due to the suspension.*

Preliminary experiments showed, moreover, that a change in potential across the conductivity cell did not cause a change of the effect (the field intensity between the plane electrodes here applied was 0.02 and 0.40 volt per cm. The development of

*Joule's* heat made the application of higher field intensities impossible). This would have been the case if an orientation effect was part of the phenomenon (cf. § 37, p. 125).

Small frequency variations did not cause a change of the effect. Electrolyte polarization was negligible at frequencies above 2000 cycles (150 000 m), as applied in most experiments with the permanent measuring arrangement. Above 10 000 cycles (30 000 m), the measurements were inaccurate due to the application of the water thermostat *etc.*, however, the conductivity effect was unchanged.

Also the conductivity of the fully dispersed suspension (the initial point of the conductivity effect) was independent of the mentioned slight change in frequency. The well-known conductivity dispersion of blood corpuscle suspensions observed by *H. Schaefer*, 1933 (366), *H. Dänzer*, 1934 (73), *F. Graul*, 1935 (161), and *K. Osswald*, 1937 (318), (cf. the survey by *B. Rajewsky*, 1938 (345)) begins at frequencies above  $1.5 \cdot 10^5$  cycles (2000 m) where the conductivity increases. At frequencies around and above  $1.5 \cdot 10^7$  cycles (20 m), the conductivity becomes again constant.

According to a number of authors (cf. *B. Rajewsky*, *loc. cit.* chapter III, p. 191), the dispersion of the conductivity in blood corpuscle suspensions must be ascribed to the building-up of the erythrocytes as dielectrics arranged in layers. That a *Debye-Falkenhagen* effect (*H. Falkenhagen*, 1932 (111) and 1935 (112)) might be the cause of the phenomenon has apparently not been taken into consideration.

The relaxation effect of colloids might possibly be the cause of the disagreement between experimental and theoretical determinations of the cataphoretic conductivity of suspensions (cf. above, § 36, p. 123). Due to relaxation in the ionic atmosphere of the colloidal particles, the electrokinetic potential calculated from *Helmholtz'* equation becomes too low (cf. the discussion between *A. Rutgers*, *J. Overbeck* and *E. Verwey*, 1938 (209, pp. 51, 52, 56 and 57)).

The phase shift which amounted on average to  $+1^\circ$  at 2000 cycles was not changed with certainty, however, it might

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\*) Addendum: Cf. *J. J. Hermans*, (113, p. 133).

increase very slightly during the course of the effect\*); *H. Fricke* and *S. Morse*, 1925/26 (134, p. 159), observed an increase. Variations of the phase angle of this minute order of magnitude could not be measured with the apparatus available. In the evaluation of the present experiments, the negligible phase angle was therefore not taken into account; the measured impedance was regarded as a pure ohmic resistance (*cf.* § 42, b., p. 176).

*c. Absolute magnitude of the conductivity effect, reversibility, and relation to blood sedimentation.*

As already observed by *H. Fricke* and *S. Morse* (*loc. cit.*), the absolute magnitude of the conductivity effect varied considerably for different blood samples. In blood samples with a very marked conductivity effect, the latter exceeded greatly *H. Fricke's* data of about 2 per cent of the conductivity of the suspension. In the case of blood sample *crt. No. 15* of experiment *K 2* (*Appendix*, p. 209), for example, the present author found a lowering of the conductivity of  $0.446 \text{ ohm}^{-1} \text{ cm}^{-1}$  after 194 sec, thus amounting to 5.3 per cent of the conductivity of the suspension ( $8.414 \text{ ohm}^{-1} \text{ cm}^{-1}$ ), and this is in no way the highest possible effect. Already in a moderately accurate conductivity determination of blood, variations in conductivity due to the mentioned effect therefore involve a considerable source of error.

It would be most rational to define the magnitude of the conductivity effect as the change in conductivity from the beginning of the phenomenon to the point of inflection which introduces the third part of the curve (in experiment *K 2*, hence, 194 sec  $0.446 \text{ ohm}^{-1} \text{ cm}^{-1}$ ). Since this point has been registered in a few measurements, only, we chose the value at an arbitrarily given time before the point of inflection. When comparing the magnitude of the conductivity effect and the sedimentation rate of blood of different arbitrary samples, a close relation between these phenomena could not be found, in spite of the fact that these tests seem to vary almost symbotically in samples of approximately the same erythrocyte concentration (*cf.* Tables *K 1*, *K 2*, *K 3*, *K 4*, *Appendix*, p. 209 a. f. p. and corresponding curves).

The conductivity effect of the individual blood sample could

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\*) *Addendum:* *Cf.*, however, the highly improved technique of *M. Trier* and *E. Warburg*, *loc. cit.* footnote p. 179.

be accurately reproduced a number of times (experiment K 1, Table K 1, *Appendix*, p. 209) until injury of the corpuscles due to stirring produced a decrease in the effect. The process which forms the basis of the effect must be completely reversible and of a very constant course. Blood with haemolysis always showed a smaller (or no) effect than uninjured blood; furthermore, the conductivity effect decreased after longer storing or short heating of the blood — in analogy to the decreasing sinking reaction after thermal stabilization. Hence, the phenomenon is conditioned by the presence of intact erythrocytes.

Since the conductivity effect

- 1) is completely dependent on the existence of intact erythrocytes,
- 2) begins immediately after cessation of stirring,
- 3) is completely reversible and may be reproduced repeatedly,
- 4) appears before sedimentation,
- 5) shows an indirect relation to the sinking reaction,

erythrocyte aggregation must be the cause of the phenomenon.

*d. The effect of an artificially promoted rouleaux formation. A conductivity effect accompanying iso-agglutination.*

If the lowered conduction was caused by a reduced degree of dispersion of the suspension, it must be possible

- I. partly to check or to promote the phenomenon by addition of substances which affect normal rouleaux formation,
- II. partly to produce the phenomenon by other types of erythrocyte aggregations apart from rouleaux formation.

Since addition of tylose (methyl cellulose) to the blood leads to a greatly increased rouleaux formation — as previously mentioned in counting- and sedimentation experiments (§ 40, d., p. 166) — the conductivity effect was measured on the same blood sample with and without addition of tylose (experiments K 3, K 12, K 13, Table K 6, *Appendix*, p. 216). The curves indicate not only a marked increase in the absolute magnitude of the effect (higher aggregation degree) but also a steeper course of the first part of the curve (increase in rate of aggregation) which

is in excellent agreement with the author's previous sedimentation experiments.

In order to prove the influence of specific agglutination (iso-agglutination) upon the conductivity phenomenon it was necessary to exclude pseudo-agglutination (rouleaux formation). While the addition of electrolytes reduced or suppressed rouleaux formation (cf. § 10, p. 23), *J. Forssman, Th. Wadstein and G. Fischer's* investigation of the influence of various salt concentrations on haemagglutination (1930 (119), already mentioned § 2, p. 7) showed that haemagglutination is not inhibited but may even be promoted by an increased salt concentration. Upon man, two types of salt effects are found, one of which is characteristic of the corpuscles of the A-group to anti-A-serum, the other one of the other groups and their anti-sera.

The author's experiments were carried out on A-corpuscles which were agglutinated equally well by anti-A-serum in 1, 3, and 5 per cent sodium chloride solution, while 5 per cent sodium chloride caused a marked reduction of agglutination in the other groups. Other alkali- and earth alkali salts in solutions which were isotonic with 1, 3, and 5 per cent sodium chloride had altogether the same effect upon the agglutinability of blood corpuscles, so that the valency of the electrolytes was without any influence; on the basis of this observation, it seems permissible to conclude that the potential of the corpuscles relative to the suspension medium is not decisive for type agglutination.

By addition of sodium chloride until slight hypertonia, rouleaux formation was completely annulled (checked microscopically) and the considerable conductivity effect of the blood decreased to zero (experiments *K 14* and *K 15*, Table *K 7*, Appendix, p. 218).

If real agglutination was produced in a weak hypertonic suspension (of A-corpuscles) by addition of type serum (test serum B with agglutinin titre 1 · 64, determined at the State's Serum Institute where the serum had been kindly put at my disposal), a change in conductivity appeared of a similar kind as in blood with rouleaux formation (experiment *K 16*, Table *K 7*, Appendix, p. 218). The microscopic control showed a clear, however not very pronounced specific agglutination but no rouleaux formation. (A theory of this experiment will be given below, § 43, f., p. 188).

The conductivity phenomenon is thus produced by erythrocyte

aggregation — either of an orientated type (normal or artificially promoted rouleaux formation) or unorientated (real agglutination). When compared with determinations of the effect in samples with varying sedimentation rates, the last mentioned experiments proved that the magnitude of the conductivity effect is founded on the aggregation degree of the suspension. Annulment of the aggregation extinguishes the phenomenon.

*e. The influence of erythrocyte concentration on the conductivity phenomenon.*

The great influence of the erythrocyte concentration on the conductivity effect was demonstrated by measurements on blood diluted with its own plasma. Experiments *K 17*, *K 18*, and *K 19*, Table *K 8*, Appendix, p. 219 illustrate the change in conductivity at three different concentrations of the same blood (pure blood, 1 part blood+1 part plasma, 1 part blood+3 parts plasma). A simple relation between dilution and conductivity effect could not be found; after dilution 1 : 2, the effect increased about four times, decreasing again after further dilution 1 : 4. At very strong dilution, the effect disappeared almost completely; moreover, we know that the effect is zero on pure plasma.

The relation between sedimentation rate and conductivity at the same erythrocyte concentration was discussed above (§ 43, p. 183). The sedimentation rate increased greatly and monotonously with increasing dilution.

*f. Theoretical explanation of the conductivity experiments. Is the effect due to "plasma occlusion" or to a change in the cataphoretic conductivity of the blood?*

An experiment carried out by *R. Fåhræus* (109, p. 106) on the sedimentation test of corpuscle-plasma suspensions proved — according to this author's interpretation — that the sedimentation rate increased with increasing dilution due to reduced friction in the suspension and, furthermore, because the aggregates became greater. If we assume a "plasma occlusion", *i. e.* erythrocyte conglomerates including some plasma, to be an essential cause of the variation in the conductivity effect with varying erythrocyte concentration (*cf.* the theoretical considerations of § 36, p. 118), the phenomenon may be interpreted on the basis

of *Fåhræus'* experiment as follows. The included amount of plasma depends on size and number of aggregates, increasing rapidly with increasing size of the aggregates, so that the same quantity of aggregates distributed over a few very large conglomerates leads to an inclusion of greater amounts of plasma than an apportion of the erythrocytes to numerous small conglomerates. When the quantity of aggregates decreases, the included plasma must decrease; moreover, the resistance-increasing effect of plasma occlusion decreases markedly with decreasing erythrocyte concentration (*cf.* *H. Fricke's* formula 72 for the conductivity, p. 116).

The influence of plasma occlusion on the sedimentation rate and the equivalent radius of conglomerates, and on the viscosity of the suspension has been mentioned repeatedly (*cf.* § 7, p. 18, § 19, p. 46, § 20, p. 52). We lack reliable information concerning the quantity of plasma included in the corpuscle conglomerates. Experiments with *S. Odén's* sedimentation balance (1915 (302), 1920 (304), and *H. Gessner*, 1931 (151, p. 88)) have not been performed. The slight difference in specific gravity of erythrocytes and plasma will probably make such an investigation difficult or even impossible.

A more stringent explanation of the influence of dilution on the conductivity phenomenon may be obtained when the effect is interpreted as a change in cataphoretic conductivity of the suspension due to erythrocyte aggregation. The cataphoretic conductivity of the suspension depends on cataphoretic velocity, on concentration, and on electric charge of the conglomerates (*cf.* § 36, p. 120). A further part plays the viscosity of the suspension which will mainly be changed by dilution.

The maximum of the effect found at a given dilution might appear by a reduced viscosity of the suspension when the viscosity decreases more rapidly in the beginning than do erythrocyte concentration and aggregation rate. When comparing the tangents of conductivity curves in their origin, we find that the steepness increases with increasing dilution. This is presumably due to an increasing contribution to the cataphoretic conductivity per single erythrocyte which "disappears" as a consequence of the decreasing viscosity of the suspension. The phenomenon hardly indicates a more rapid aggregation.



Also the previously mentioned conductometrical experiments may be explained on the basis of the theory of the cataphoretic conductivity of suspensions. The increase of the effect with the degree of aggregation becomes directly comprehensible (*cf.* § 36, p. 121). The conductivity decreases with increasing electrolyte concentration (*cf.* experiment *K 15*, *Appendix*, p. 218) due to reduced aggregation, migration velocity, and number of charges of the particles. The reduction of the two last mentioned factors must be ascribed to lowered electrokinetic potential (reduced thickness of the electric double layer).

The relatively small effect in agglutinin experiments (*cf.* experiment *K 16*, *Appendix*, p. 218) is due to different factors, apart from the described effect of an increased electrolyte concentration it must be ascribed to the binding of the iso-antisubstance to the corpuscles whose potential is thereby reduced. In B-serum, the A-corpuscles lose 25 per cent of their potential (*V. Schröder*, 1926 (373), *C. Pulcher*, 1933 (342)). If rouleaux formation had not been inhibited by addition of sodium chloride, also the rouleaux-promoting effect of the thermo-denaturated protein of the test serum should have been taken into account; during preparation, the test serum is heated to 56°C in order to destroy natural haemolysins which make fresh serum inapplicable to experiments.

*g. Temperature dependence of the conductivity effect.*

Most determinations of the conductivity effect were carried out at the arbitrarily chosen temperature of 24°.90 C. The influence of temperature on the effect was studied in measurements of the same blood sample (crt. No. 9, *Appendix*, p. 198) and at the temperatures 11°.20, 24°.90, and 37°.60 C (experiments *K 21*, *K 6*, *K 20*, Table *K 9*, *Appendix*, p. 221). In the case of fully dispersed suspensions, the conductivity was a linear function of temperature in the range investigated. The increase in conductivity per degree Celsius was  $0.142 \text{ ohm}^{-1} \text{ cm}^{-1}$ . The conductivity effect increased considerably with temperature and amounted to

0.180 $\text{ohm}^{-1} \text{ cm}^{-1}$	at	11°.20 C
0.218 $\text{ohm}^{-1} \text{ cm}^{-1}$	at	24°.90 C
0.308 $\text{ohm}^{-1} \text{ cm}^{-1}$	at	37°.60 C,

respectively, after the course of 60 sec. It has been mentioned previously (cf. § 23, p. 60) that the cataphoretic migration velocity of different particles increases with rising temperature and inversely proportional to the viscosity of the dispersion medium. Although the author could not find any description of similar experiments with red corpuscles in the literature available, it seems reasonable to consider the increase of the effect to be mainly caused by changes in viscosity of the suspension.

In experiments concerning the temperature effect, a peculiar phenomenon has been observed, *viz.* that the steepness of the tangent in the origin of the conductivity curve decreases with increasing temperature in spite of reduced viscosity. The aggregation velocity of the erythrocytes which mainly determines the course of the conductivity effect decreases (as already shown in § 40, c., p. 166) with increasing temperature, presumably due to changes in the electric double layer of the erythrocytes. We must therefore assume that the influence of viscosity alterations on the conductivity effect can initially not compensate the influence of the temperature sensitivity of the aggregation.

#### *h. The paradoxical conductivity phenomenon.*

The peculiar effect of dilution on the conductivity phenomenon reminds us of the so-called "paradoxical" effect, since also this phenomenon is presumably due to variations in viscosity of the suspension. When measuring the cataphoretic effect, we sometimes meet with an initial reduction of resistance (3 among 73 cases, hence c. 4 per cent) which later is reverted into an increase in resistance (cf. experiments *K* 22 and *K* 23, *Appendix*, p. 222).

The first experiment in which the paradoxical effect was observed is omitted in the tables because of incomplete data; this experiment was primarily regarded as failed (the erythrocyte count was 5.10 Mill. per mm<sup>3</sup>, and the sedimentation test was 1.5 mm per hour). The paradoxical effect could be reproduced repeatedly on the same blood sample; it could not be ascribed to accidental sources of error such as electrolyte polarization and the like. At a suitable dilution of the suspension, a conductivity effect of normal type was obtained (cf. experiment 24, *Appendix*, p. 223).

The paradoxical conductivity effect might appear as a conse-

quence of viscosity alterations in the aggregating suspension, since weak aggregation might cause a strong reduction of viscosity of the suspension so that the cataphoretic conductivity is increased.

*i. The conductivity phenomenon as an expression of polydisperse coagulation.*

In previous investigations of the aggregation process in dilute corpuscle-plasma suspensions by means of the counting method (cf. § 40, a., p. 160), the author was able to prove that rouleaux formation is a very markedly polydisperse coagulation. Moreover, the author's observations concerning iso-agglutination proved that also the latter is an intensely polydisperse coagulation.

When curves of the conductivity effect are compared with coagulation curves (number of particles as axis of ordinates, time as axis of abscissae) of a concentrated polydisperse system, we find a striking similarity, since the steep part of the conductivity curve corresponds to beginning coagulation where the number of particles decreases rapidly due to real polydisperse coagulation, while the slightly decreasing last part of the conductivity curve represents the slow phase of coagulation, a monodisperse coagulation which indicates the complete disappearance of single particles.

*H. Fricke* and *S. Morse* (133) observed a phenomenon in cream which corresponded to the conductivity effect in blood; also cream shows a pronounced polydisperse coagulation (cf. *Wiegner-Galecki* effect, § 28, p. 75). This observation seems to confirm the above interpretation.

*j. The influence of stirring on the cataphoretic conductivity effect.*

*L. Berczeller* and *H. Wastl's* investigations of the influence of shaking and streaming on the sedimentation test, 1923 (27) and 1924 (28), and *E. Sigman*, *A. Kolin*, *L. N. Katz* and *K. Jochim's* experiments with flowing blood, 1937 (378), have been mentioned above (cf. § 19, p. 49 and § 32, p. 95, respectively). The author's coagulation measurements on dilute corpuscle-plasma suspensions carried out by means of the counting method (cf. § 40, e.,

p. 167) demonstrated the influence of shaking on aggregation in full agreement with *Smoluchowski's* interpretation. For a further study of these phenomena on whole blood, the conductometrical method was found especially suited.

When the stirrer was started after the measurement of the conductivity effect, a short-lasting but marked increase in the effect appeared during the very first moments, which was followed by a rapid increase in conductivity to the initial value.

With respect to the effect of stirring on the aggregation process, two types of experiments were performed, *viz.* measurements of the effect

- I. of a transition from different rate of stirring to complete rest, similar to normal coagulation experiments, and
- II. of a sudden transition from the critical rate of stirring which produces full dispersion of the erythrocytes to a lower rate of stirring.

Experiments of type I (*cf.* experiments *K 25, K 17, K 26, Table K 11, Appendix, p. 224*) proved that the effect reached a maximum at a certain rapid (critical) rate of stirring and was not further increased when stirring was increased. At a lower rate of stirring than the critical one, the steep part of the curve was found to be shortened, *i. e.* aggregation started with a speed corresponding to the momentaneous aggregation degree of the suspension.

Experiments of type II (*cf.* experiments *K 27, K 28, K 29, Table K 12, Appendix, p. 224*) showed that a minimum stirring already produced very marked acceleration of the coagulation. At a given, relatively low rate of stirring, a considerable increase in coagulation and a maximum increase in the degree of aggregation could be observed. Subsequently, the final degree of aggregation decreased even when the initial rate of coagulation was further increased. The upper limit of the degree of aggregation was determined by the rate of stirring, *i. e.* dynamical equilibrium was attained between conglomeration caused by the spontaneous tendency to aggregation of the erythrocytes which was promoted by particle convection ensuing stirring, and disaggregation of conglomerates as a consequence of stirring.

*k. Interpretation of E. Sigman, A. Kolin, L. N. Katz and K. Jochim's experiment on the basis of the author's own measurements.*

In streaming experiments carried out by the mentioned authors (378) (cf. § 32, p. 95), the degree of aggregation of the blood in the container was rather poorly defined because of storing for varying time and inconstant stirring. The effects measured on flowing blood depended on the aggregation degree in the container. In the author's experiments, the initial state was well-defined, since the suspension was monocellular. The "electrode effect" observed by *Sigman, Kolin, Katz and Jochim* has neither to do with the electrodes nor with a counteraction of the aggregation process by streaming, but can actually be explained by the aggregation-promoting effect of slow currents. If the corpuscles are almost completely dispersed so that the electrode effect is very marked, the effect of streaming must be small, since an increased rate of flow can only give rise to a splitting of small conglomerates. According to our present knowledge, the reduced "flow effect" during specific haemagglutination must presumably be ascribed to a lower degree of aggregation in the sample containing serum of another type relative to the control sample with normal rouleaux formation. Furthermore, the lowered electrokinetic potential of the corpuscles due to binding of iso-agglutinin plays a minor rôle (cf. above p. 188 *V. Schröder* (373)).

*l. The influence of the gas content of the blood on the conductivity phenomenon.*

After the conductivity effect had been measured in the usual way on blood which was brought in gaseous equilibrium with the atmosphere by slight shaking in a flat dish for c. 10 min., the effect was measured on the same sample after saturation with expiration air (alveolar air) (cf. experiment *K 30*, Table *K 13*, Appendix, p. 225). Within the experimental error, no difference between the measured effects was found. The change in  $p_H$  is not considerable (from  $p_H$  c. 8 to  $p_H$  c. 7). If we assume — in agreement with *H. A. Abramson* and *L. Moyer*, 1936 (7), and *G. Hevesy*, 1917 (196) — that the charge density of the particles, i. e. their number of charges per surface unit, remains constant despite the increase in surface, the slight decrease in aggrega-

tion due to the  $p_H$  variation will be compensated. A saturation of the blood with carbon dioxide is unphysiological, since it would change the situation completely due to a stronger deformation of the corpuscles to spherocytes.

*m. Concluding remarks concerning the results of conductometric experiments.*

Since the interpretation of the conductivity effect as change in cataphoretic conductivity of the suspension due to erythrocyte aggregation has proved very useful to explain a number of experimental facts, we may expect that the charge of the erythrocytes is greater than the value calculated by *H. A. Abramson* and *L. Moyer* (7), (*cf.* § 23, p. 62 and § 36, p. 124).

#### D. OTHER EXPERIMENTS.

#### § 44. INVESTIGATIONS CONCERNING A METABOLISM HYPOTHESIS.

According to a theory by *N. Rashevsky*, 1931/32 (348) and 1938 (349), the in- or out-diffusing metabolism products of animal or vegetabil cells\*) can form inhomogeneous fields of concentration around the cells in the suspension medium and thereby give rise to mutual actions between the cells with resulting as well as torquing forces.

In the case of spherical and ellipsoidal particles, *G. Young*, 1936 (454), and *G. Young* and *J. Reiner*, 1937 (455), have given an elegant mathematical treatment. However, these calculations are based upon the assumption of an osmotic pressure per surface element proportional to the local concentration of the metabolism products. *S. Levine* and *G. P. Dube*, 1939 (252, p. 1137), emphasized (*cf.* the critical remarks of these authors concerning a corresponding application by *I. Langmuir*, 1938 (243)) that this assumption is only admissible if the surface planes are permeable to water and if the water molecules can only pass across the surface planes, but cannot escape as in suspensions of discrete particles (*cf.*, furthermore, *S. S. Kistler's* coagulation theory, 1932 (226), § 23, p. 63). For the measurement of forces

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\*) As regards the agglutination of yeast cells, *cf.* *N. Nielsen*, 1931/33 (295).

between the cells, *N. Rashevsky* (*loc. cit.*) suggested kinematographic photographs.

A number of aerobic and anaerobic metabolism processes occur in erythrocytes to a greater or smaller extent, glycolysis being the best-known of these processes (*cf. E. Lundsgaard*, 1933 (267)). Without going into further details of *N. Rashevsky's* theory, we may say the following about erythrocytes. If metabolism products from the mentioned processes should be of importance for rouleaux formation by producing an unequal concentration distribution around the corpuscles, it should be possible to affect aggregation by addition to the blood of substances which interfere with this metabolism.

From the investigations of cell metabolism, we know a number of chemical compounds which inhibit or promote some of the partial processes, completely suppress other processes, or cause a transition from aerobic to anaerobic metabolism, and *vice versa*. These effects have therefore been studied partly by addition of poisons such as fluoride (*cf. Table S 1, Appendix*, p. 227), cyanide (*Table S 2, Appendix*, p. 229), azide (*Table S 3, Appendix*, p. 230), carbon monoxide (*Table S 4, Appendix*, p. 231), and moniodo acetate (*Table S 5, Appendix*, p. 232), partly by addition of substrate in amounts exceeding that normally present in the form of glucose (*Table S 6, Appendix*, p. 233), and finally by addition of an intermediary metabolism product as fumaric acid (*Table S 7, Appendix*, p. 234). (Maleinic acid has not been tried). Hydrogen sulfide (*Table S 8, Appendix*, p. 235) which might affect the metabolism in various ways has also been tested. The sedimentation test of a series of blood samples after addition of one of the mentioned substances was compared with the sedimentation test of ordinary oxalate blood.

In order to saturate blood with carbon monoxide (kitchen gas) and hydrogen sulfide, an *Erlenmeyer* flask was provided with in- and outlets, and the flask containing a blood sample was filled with the respective gas. After slight shaking of the blood along the walls of the flask, a new quantity of the gas was led in, *etc.* A hobbling gas-stream could not be applied because of foam formation. The solutions of cyanide, azide, moniodo acetate, and fumaric acid contained the usual amount of potassium oxalate (20 per cent) as anti-coagulant. The concentration of

the solutions was chosen so that addition of 0.1 cc of the solution to 8 cc blood (after blood letting) gave the following concentrations of the respective substance.

Potassium cyanide . . . . .	0.0077 molar	(Table S 2)
Sodium azide . . . . .	0.001 molar	(Table S 3)
Potassium monoiodo acetate. . . . .	0.0001 molar	(Table S 5, sol.I)
Potassium monoiodo acetate. . . . .	0.0002 molar	(Table S 5, sol.II)
Glucose, increase of . . . . .	0.1 per cent	(Table S 6)
Fumaric acid . . . . .	0.001 molar	(Table S 7)

In the case of fluoride which simultaneously acts as an anti-coagulant due to its ability to bind calcium, only potassium fluoride solutions were applied, *viz.* 0.1 cc per 8 cc blood. Hence

Potassium fluoride . . . . .	0.027 molar	(Table S 1).
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All chemicals investigated, except fluoride, were without any influence on the sedimentation rate. Fluoride blood showed a markedly inhibited sinking relative to control oxalate blood.

The fact that fluoride suppresses glycolysis cannot be considered the cause of the reduced blood sedimentation, as in this case the sinking reaction should decrease with decreasing intensity of glycolysis. According to *W. A. Engelhardt* and *U. Ljubimowa*, 1930 (105), the glycolysis intensity in the corpuscles of different animal species decreases in the following series, *viz.* rabbit, man, Guinea-pig, horse, dog, goat, ox. This series is not at all the same as the sequence of the normal sedimentation rate of these animal species.

For the calculation of the calcium ion concentration of blood after addition of a given amount of a very soluble oxalate or fluoride, the ordinary method of the solubility product is inapplicable, since a complete precipitation of the slightly soluble salt does not occur. This was already realized by *H. Lebel*, 1939 (245), who determined the calcium ion concentration in serum by investigating the solubility of a slightly soluble calcium salt. Both salts mentioned above, calcium fluoride even to a still higher extent than calcium oxalate, show a tendency to form supersaturated solutions, so that the respective solubility product must be exceeded several times before precipitation occurs. (With regard to calcium fluoride, *cf. A. Tovborg Jensen*, 1937 (212); with regard to calcium oxalate, *cf. G. Hammarsten*, 1928 (174), and *K. J. Pedersen*, 1939 (326)). The presence of colloids can furthermore promote the formation of supersaturated solutions.



At the time being, it is impossible to perform a precise calculation of the calcium ion concentration, but the greater tendency of calcium fluoride to form supersaturated solutions allows us to conclude that the calcium ion concentration is greater in fluoride than in oxalate blood at the concentrations of the salts here applied. With the inhibition of rouleaux formation by divalent calcium ions *in mente* (cf. J. Runnström, 1921 (362), and Uehara, 1929 (424), § 10, p. 24), we understand the retarded sinking reaction of fluoride blood. Owing to the higher calcium ion concentration of fluoride blood, the latter gave frequently coagulating samples while the same hardly ever occurred with oxalate blood.

# APPENDIX.

Tables and Curves.

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Blood samples crt. Nos. 1—11.

*Ordinary blood investigations*  
of the oxalate blood samples employed for aggregation experiments and conductivity measurements.

Blood sample Crt. No., No. Date	Used in exp. No.	Sex Clin. Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mill/mm <sup>3</sup>	Colour index	Leucocyte number per mm <sup>3</sup>	Sedimentation test in mm/hour at 20° C.
1. 617 21—1—39	A 17	♀ Simple anaemia	F. H. <sup>1)</sup> Dep. E. amb.	82	4.30	0.95	8000	3
2. 836 14—2—39	A 5—7	♂ Cancer of esophagus	R. St. <sup>2)</sup> Dep. III No. 13072	76	3.68	1.03	8760	19
3. 621 23—2—39	A 2—4	♀ Chron. ar- tic. rheu- matism	F. H. Dep. E. amb.	76	4.38	0.87	6200	23 <sup>3)</sup>
4. 675 25—2—39	A 22 A 1	♀ Chron. artic. rheumatism	No. 1936 F. H. Dep. E 1 No. 5252	61	3.80	0.80	7200	39 <sup>3)</sup>
5. 741 10—6—39	A 20 A 21	♀ Simple anaemia	F. H. Otol. Dep. No. 67/1939	79	3.98	0.99	6800	2
6. 838 12—6—39	K 3 K 12 K 13	♂ Simple anaemia	F. H. Dep. E. amb.	84	4.70	0.89	7640	7
7. 855 13—6—39	K 9	♀ Observ. for artic. rheumatism	No. 3355 F. H. Dep. E. amb.	94	5.35	0.88	6600	8
8. 806 14—6—39	K 11	♀ Pernicious anaemia	No. 5851 F. H. Otol. Dep.	53	2.03	1.29	6160	12
9. 410 17—6—39	K 6 K 20 K 21	♀ Indurat. tuberculosis of leg	F. H. Dermat. Dep.	86	5.06	0.85	9280	5
10. 432 21—6—39	K 1	♀ Cancer of cervix uteri	No. 81722 R. St. No. 13331	74	3.64	1.01	4840	24
11. 447 22—6—39	K 10 A 14 —15	♀ Articular rheumatism	F. H. Dep. E. No. 4677	76	4.13	0.92	9800	55 <sup>3)</sup>

<sup>1)</sup> F. H. = Finsen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

Blood samples crt. Nos. 12—24.

*Ordinary blood investigations*  
of the oxalate blood samples employed for aggregation experiments and  
conductivity measurements. (Contin.)

Blood sample Crt. No., No. Date	Used in exp. No.	Sex Clin. Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mill/mm <sup>3</sup>	Colour index	Leucocyte number per mm <sup>3</sup>	Sedimentation test in mm/hour at 20° C.
12. 11—8—39	K 17 —19 K 25 —29	♂ Healthy	F. L. <sup>4)</sup> amb.	105	5.38	0.97		2
13. 16—8—39	K 5	♂ Vincent's angina	F. H. <sup>1)</sup> Dep. E. No. 5976	84	4.77	0.88		88
14. 11—9—39	K 14 —16	♂ Healthy	F. L. amb.	100	4.93	1.01		2
15. 913 12—10—39	K 2	♂ Sarcoma of the pubis	R. St. <sup>2)</sup> amb. No. 20125	56	3.54	0.71	10980	137
16. 757 14—10—39	K 22	♂ Artrit. de- form. of spine	F. H. Surg. Dep. amb. No.k/16465	88	5.00	0.88	6600	2
17. 748 16—10—39	K 7	♂ Cervical adenitis	F. H. Surg. Dep. No.k/16467	92	5.09	0.90	7640	24
18. 852 18—10—39	K 8	♂ Vasomotor. rhinitis	F. H. Otol. Dep. amb.	99	5.20	0.95	7800	4
19. 827 20—10—39	K 4 K 30	♂ Cancer of mandible	R. St. amb. No. 20887	84	4.77	0.88	6240	16
20. 20—10—39	K 23 —24	♂ Healthy	F. L. amb.	107	5.40	0.99	4570	2
21. 656 8—11—39	A 16 A 8—9	♀ Sequels of otitis media	F. H. Otol. Dep. amb.	90	4.07	1.11	6520	2
22. 740 10—11—39	A 19 A 12 —13	♀ Cancer of maxilla	R. St. amb. No. 21473	86	4.41	0.97	7120	45 <sup>3)</sup>
23. 452 20—11—39	A 18	♂ Cancer of tongue, operated	R. St. amb. No. 18340	85	4.31	0.99	10200	17
24. 454 22—11—39	A 10 —11	♂ Bronchial asthma	F. H. Dep. E 1 No. 5110	87	4.28	1.01	4880	9

<sup>1)</sup> F. H. = Finsen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

<sup>4)</sup> F. L. = Finsen Laboratory.

Experiment A 1. Tables A 1 a and A 1 b.

## A. AGGREGATION EXPERIMENTS.

Experiment A 1. February 25th, 1939.

Oxalate blood. Sample crt. No. 4.

Erythrocyte count: 3.80 mill./mm<sup>3</sup>.

Sedimentation test: 39 mm/hour (diffuse interface)

Blood-plasma dilution: 1 : 75.

Temperature: 20°C.

Table A 1 a.

Comparison of "rouleaux formation" and Smoluchowski coagulation.

	Time in sec.	$\nu_0$	$\Sigma\nu$	$\nu_1$	$\nu_2$	$\nu_3$	$\nu_4$	$\nu_5$	$\nu_6$	$\nu_7$	$\nu_8$
Experiment A 1. Smoluchowski coagulation ....	600	1498	735	575	34	16	14	17	19	17	12
	4514	1498	929	575	220	82	32	13	5	2	0
		$\nu_9$	$\nu_{10}$	$\nu_{11}$	$\nu_{12}$	$\nu_{13}$	$\nu_{14}$	$\nu_{15}$	$\nu_{16}$	$\nu_{17}$	$\nu_{18}$
Experiment A 1. Smoluchowski coagulation ....	600	10	11	2	1	2	2	0	2	1	0
	4514	0	0	0	0	0	0	0	0	0	0

Table A 1 b.

	$R/r$ calculated from $\Sigma\nu$ and $\nu_1$	$R/r$ calculated from $\nu_0$ and $\nu_1$	$R/r$ calculated from $\nu_0$ and $\Sigma\nu$
Experiment A 1.	5.3 ( $T=2756$ sec.)	15.4 ( $T=980$ sec.)	20.2 ( $T=578$ sec.)
Smoluchowski coagulation .....	2.0 ( $T=7370$ sec.)	2.0 ( $T=7370$ sec.)	2.0 ( $T=7370$ sec.)

For the calculation of  $R/r$  in tables A 1 b, A 2 b, A 3, A 4, A 5 a, and A 9 b, the plasma viscosity was arbitrarily put to 0.02 Poise at 20°C. (cf. § 40 a., p. 162), because corresponding measurements were not performed. However, the plasma viscosity varies to some extent in different blood samples.

Experiments A 1 contin., A 2—A 4. Tables A 1 c, A 2 a.

Table A 1 c.

Number of aggregates of a given size per square.  
(1498 erythrocytes counted in 10 squares).

Aggre- gate	Number of aggregates per square										Total num- ber	Ave- rage per square
	1	2	3	4	5	6	7	8	9	10		
$\nu_1$	71	66	58	64	56	55	49	55	46	55	575	58
$\nu_2$	4	2	1	3	3	4	7	4	4	2	34	3
$\nu_3$	1	1	0	0	2	2	1	2	4	3	16	2
$\nu_4$	1	2	3	0	2	2	0	0	2	2	14	1
$\nu_5$	0	0	1	2	1	4	3	2	1	3	17	2
$\nu_6$	3	1	2	2	1	3	2	1	3	1	19	2
$\nu_7$	3	2	1	3	1	1	1	2	1	2	17	2
$\nu_8$	1	3	1	1	1	1	0	2	1	1	12	1
$\nu_9$	0	1	0	3	0	2	1	1	2	0	10	1
$\nu_{10}$	0	0	3	1	2	1	4	0	0	0	11	1
$\nu_{11}$	0	0	0	0	0	0	0	0	2	0	2	0
$\nu_{12}$	0	0	0	0	0	0	1	0	0	0	1	0
$\nu_{13}$	0	0	1	0	0	0	0	0	0	1	2	0
$\nu_{14}$	0	0	0	1	0	0	0	0	1	0	2	0
$\nu_{15}$	0	0	0	0	0	0	0	0	0	0	0	0
$\nu_{16}$	1	0	0	0	0	0	0	0	0	1	2	0
$\nu_{17}$	0	0	0	0	0	0	0	0	0	1	1	0
$\nu_0$	149	134	147	172	122	158	161	124	166	165	1498	150
$\Sigma \nu$	85	78	71	80	69	75	69	69	67	72	735	73

Experiments A 2, A 3, A 4. February 23rd, 1939.

Oxalate blood. Sample crt. No. 3.

Erythrocyte count: 4.38 mill./mm<sup>3</sup>.

Sedimentation test: 23 mm/hour (diffuse interface)

Blood-plasma dilution: 1 : 75.

Temperature 20°C.

Table A 2 a.

Variation in the size of aggregates with time.

Experiment	$t$	$\nu_0$	$\nu_1$	$\Sigma \nu$	$\nu_2$	$\nu_3$	$\nu_4$	$\nu_5$	$\nu_6$	$\nu_7$
A 2	300	722	482	533	6	9	9	9	11	2
A 3	420	806	361	433	5	7	13	7	9	7
A 4	600	775	283	372	14	11	12	10	17	5
Experiment	$\nu_8$	$\nu_9$	$\nu_{10}$	$\nu_{11}$	$\nu_{12}$	$\nu_{13}$	$\nu_{14}$	$\nu_{15}$	$\nu_{16}$	
A 2	5	0	0	0	0	0	0	0	0	
A 3	11	6	4	1	0	0	0	1	1	
A 4	7	5	3	2	0	1	1	0	1	

Experiments A 2—A 4 contin., A 5—A 9. Tables A 2 b, A 3, A 4.

Table A 2 b.  
Experiments A 2—A 4.

$R/r$ Calculated from	At the time		
	300 sec.	420 sec.	600 sec.
$\Sigma v$ and $v_1$	4.5	6.1	6.7
$v_0$ and $v_1$	9.5	15.0	14.0
$v_0$ and $\Sigma v$	15.1	26.2	23.1

Experiments A 5, A 6, A 7. February 14th, 1939.

Oxalate blood. Sample crt. No. 2.  
Erythrocyte count: 3.68 mill./mm<sup>3</sup>.  
Sedimentation test: 19 mm/hour.  
Temperature: 20°C.

Table A 3.

Experiment No.	Time in sec.	Blood-plasma dilution	Notation of aggregate			$R/r$ calculated from $v_1$ and $\Sigma v$
			$v_1$	Conglom.	$\Sigma v$	
A 5	435	1 : 50	261	80	341	7.1
A 6	435	1 : 75	320	59	379	6.5
A 7	435	1 : 100	369	17	386	2.1

Experiments A 8, A 9. November 8th, 1939.

Oxalate blood. Sample crt. No. 21.  
Erythrocyte count: 4.07 mill./mm<sup>3</sup>.  
Sedimentation test: 2 mm/hour.  
Blood-plasma dilution: 1 : 75.  
Temperature 20°C.

Table A 4.

Distribution of particles during "slow" rouleaux formation.

Experiment No.	$t$	$v_0$	$v_1$	$\Sigma v$	$\Sigma v_{2, n}$	$v_2$	$v_3$	$v_4$	$v_5$	$v_6$	$v_7$	$R/r$ calculated from $v_0$ and $\Sigma v$
A 8	300	678	645	657	12	6	4	1	1	0	0	1.5
A 9	600	725	650	671	21	5	7	4	3	1	1	1.8

If the formation of conglomerates occurred according to Smoluchowski,  $R/r$  calculated from  $v_0$  and  $\Sigma v$  would be somewhat less than the values given, since  $\Sigma v$  becomes greater on account of several less composed aggregates.

$R/r < 1$  is in good agreement with the interpretation of the process investigated as "slow" coagulation.

Experiments A 2, A 4, A 8—A 15. Tables A 5 a, A 5 b.

Table A 5 a.

Relation between sedimentation test and erythrocyte aggregation.

Experiment No. Date	Blood sample No.	Erythro- cyte count mill./mm <sup>3</sup>	Sediment- ation test mm/hour	After 300 sec.			After 600 sec.		
				$v_0$	$\Sigma v$	$R/r$	$v_0$	$\Sigma v$	$R/r$
A 8 and A 9 8—11—39	21	4.07	2	678	657	1.5	725	671	1.8
A 10 and A 11 22—11—39	24	4.28	9	709	646	4.3	763	576	7.1
A 2 and A 4 23—2—39	3	4.38.	23 <sup>1)</sup>	722	533	15.1	775	372	23.1
A 12 and A 13 10—11—39	22	4.41	45 <sup>1)</sup>	737	518	17.9	790	328	29.8
A 14 and A 15 22—6—39	11	4.13	55 <sup>1)</sup>	684	463	21.5	735	291	34.4

All experiments were carried out with a blood-plasma dilution 1 : 75.

Temperature: 20°C.

<sup>1)</sup> Diffuse interface.

Table A 5 b.

Aggregation distribution at  $t = 300$  seconds.

Experiment No.	$v_0$	$v_1$	$\Sigma v$	$v_2$	$v_3$	$v_4$	$v_5$	$v_6$	$v_7$	$v_8$	$v_9$	$v_{10}$	$v_{11}$	$v_{12}$	$v_{13}$	$v_{14}$
A 8	678	645	657	6	4	1	1	0	0	0	0	0	0	0	0	0
A 10	709	622	646	6	6	5	5	2	0	0	0	0	0	0	0	0
A 2	722	482	533	6	9	9	9	11	2	5	0	0	0	0	0	0
A 12	737	460	518	9	10	11	9	8	6	5	0	1	0	0	0	0
A 14	684	406	463	7	13	10	8	6	4	6	0	1	1	1	0	0



Experiments A 4, A 9, A 11, A 13, A 15—19. Tables A 5 c, A 6.

Table A 5 c.

Aggregation distribution at  $t = 600$  seconds.

Experiment No.	$\nu_0$	$\nu_1$	$\Sigma \nu$	$\nu_2$	$\nu_3$	$\nu_4$	$\nu_5$	$\nu_6$	$\nu_7$	$\nu_8$	$\nu_9$
A 9	725	650	671	5	7	4	3	1	1	0	0
A 11	763	525	576	8	9	6	11	9	4	2	2
A 4	775	283	372	14	11	12	10	17	5	7	5
A 13	790	233	328	13	15	10	12	10	8	8	6
A 15	735	205	291	7	12	11	10	11	8	7	7

Experiment No.	$\nu_{10}$	$\nu_{11}$	$\nu_{12}$	$\nu_{13}$	$\nu_{14}$	$\nu_{15}$	$\nu_{16}$	$\nu_{17}$	$\nu_{18}$	$\nu_{19}$
A 9	0	0	0	0	0	0	0	0	0	0
A 11	0	0	0	0	0	0	0	0	0	0
A 4	3	2	0	1	1	0	1	0	0	0
A 13	4	3	2	2	1	1	1	0	0	0
A 15	3	4	2	0	1	0	1	1	0	0

Table A 6.

Experiment No. Date	Blood sample No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour	Blood-plasma dilution	Degree of aggregation after 10 min. at		
					5°C.	15°C.	30°C.
A 16 8-11-39	21	4.07	2	1 : 75	++	+	+
A 17 21-1-39	1	4.30	3	1 : 75	+++ <sup>1)</sup>	+	+
A 18 20-11-39	23	4.31	17	1 : 75	+++	++	+
A 19 10-11-39	22	4.41	45 <sup>2)</sup>	1 : 75	++++	+++	++

<sup>1)</sup> Cold-agglutinin.

<sup>2)</sup> Diffuse interface.

Experiments A 20, A 21. Tables A 7, A 8.

*Experiment A 20.* June 10th, 1939.

The mixtures described below were prepared from the original solutions:

I. Whole blood-plasma dilution 1 : 20 from blood sample crt. No. 5.

II. Isotonic glucose solution.

III. Isotonic glucose solution with 1 per cent tylose.

The degree of aggregation observed after 10 min. is marked with an increasing number of plus signs. The final blood dilution was 1 : 100.

*Table A 7.*

Influence of the tylose concentration on aggregation.

Composition of the suspension	Degree of aggregation after 10 min.
1) 0.5 cc I. + 2.0 cc II. + 0.0 cc III.	+
2) 0.5 cc I. + 1.6 cc II. + 0.4 cc III.	++
3) 0.5 cc I. + 1.2 cc II. + 0.8 cc III.	++
4) 0.5 cc I. + 0.8 cc II. + 1.2 cc III.	+++
5) 0.5 cc I. + 0.4 cc II. + 1.6 cc III.	+++
6) 0.5 cc I. + 0.0 cc II. + 2.0 cc III.	++++

*Experiment A 21.* June 10th, 1939.

I. Undilute oxalate blood (sample crt. No. 5).

II. 5 cc blood + 1 cc isotonic glucose solution.

III. 5 cc blood + 1 cc isotonic glucose solution with 0.5 per cent tylose.

IV. 5 cc blood + 2 cc isotonic glucose solution.

V. 5 cc blood + 2 cc isotonic glucose solution with 0.5 per cent tylose.

*Table A 8.*

Sedimentation rate of blood with and without tylose.

Time in min.	Sedimentation rate in mm of the mixture No.				
	I.	II.	III.	IV.	V.
0	0	0	0	0	0
8	—	—	—	—	3
10	—	—	2	—	—
13	—	—	3½	—	10
15	1	1	—	1½	—
18	—	—	6½	—	21½
23	—	—	11	—	38
28	—	—	16	—	55
33	1½	1½	23	1¾	71
38	—	—	29½	—	87
43	—	—	37	—	99
48	—	—	44	—	107
53	—	—	50¾	—	—
60	2	2	59	2½	114

Extrapol. time of aggregation

ca. 17

ca. 11 min.

## Experiment A 21.

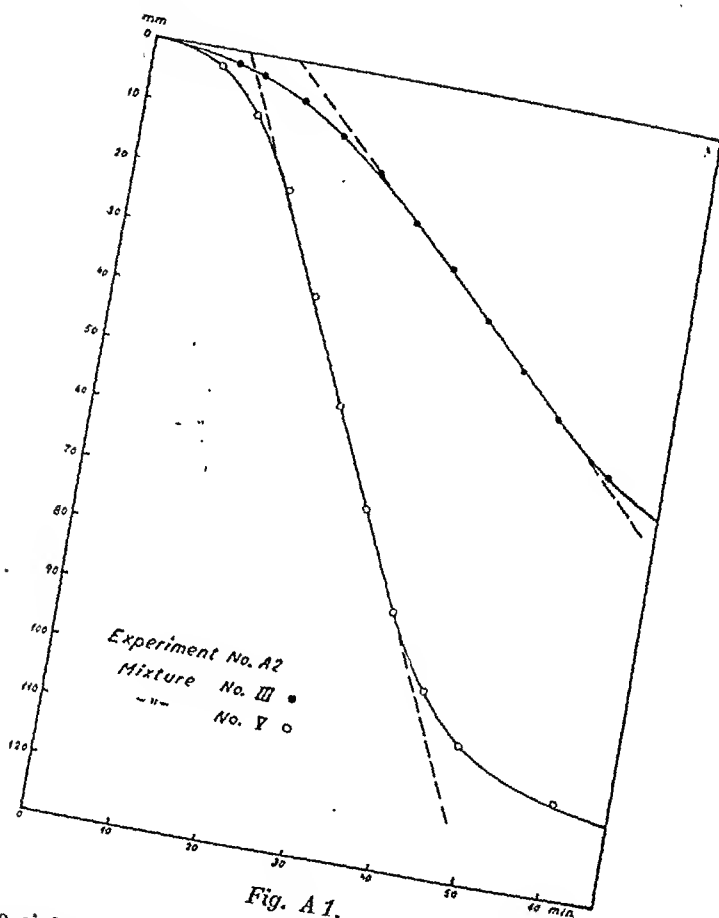


Fig. A 1.

Curves of the sinking reaction in blood samples containing tylose (experiment A 21: mixtures III and V).  
Ordinates: sinking in mm. Abscissae: time in min.  
The time of aggregation of the samples was determined by graphic extrapolation (cf. § 19, p. 46).

Experiments A 1, A 22. Tables A 9 a, A 9 b.

Experiment A 22. February 25th, 1939.

Blood sample ert. No. 4.

Erythrocyte count: 3.80 mill./mm<sup>3</sup>.

Sedimentation test: 39 mm/hour (diffuse interfaec).

Blood-plasma dilution: 1 : 75.

Time: 600 sec.

Temperature: 20°C.

Experiment A 22 was performed during slight shaking of the suspension. In Table A 9 a, particle countings of this sample are compared with countings of experiment A 1 which was carried out on the same blood sample and under the same conditions, however, without shaking of the suspension.

Table A 9 a.

	$\nu_0$	$\Sigma \nu$	$\nu_1$	$\nu_2$	$\nu_3$	$\nu_4$	$\nu_5$	$\nu_6$	$\nu_7$	$\nu_8$	$\nu_9$	$\nu_{10}$	$\nu_{11}$
Experiment A 1 (without shaking)	1498	735	575	34	16	14	17	19	17	12	10	11	2
Experiment A 22 (with shaking)	1513	383	201	28	13	12	22	17	17	17	12	10	6

	$\nu_{12}$	$\nu_{13}$	$\nu_{14}$	$\nu_{15}$	$\nu_{16}$	$\nu_{17}$	$\nu_{18}$	$\nu_{19}$	$\nu_{20}$	$\nu_{21}$	$\nu_{22}$	$\nu_{23}$	$\nu_{24}$	$\nu_{25}$
Experiment A 1 (without shaking)	1	2	2	0	2	1	0	0	0	0	0	0	0	0
Experiment A 22 (with shaking)	5	7	1	5	3	2	1	1	0	0	1	1	1	0

Table A 9 b.

	$R/r$ calculated from $\Sigma \nu$ and $\nu_1$	$R/r$ calculated from $\Sigma \nu$ and $\nu_0$
Experiment A 1 (without shaking)	5.3 ( $T = 2756$ sec.)	20.2 ( $T = 578$ sec.)
Experiment A 22 (with shaking)	11.7 ( $T = 1263$ sec.)	72.5 ( $T = 203$ sec.)

## B. CONDUCTIVITY MEASUREMENTS.

### Determination of the cell constant<sup>1)</sup>.

#### Conductivity cell I.

*N*/10 potassium chloride solution.

Temperature 24°.90 C.

Frequency 2000 cycles.

Adjustment  $N = 100$   $Z = 50$   $\phi = 0^\circ$ .

Measurement  $Z = 50.3$  ( $\phi = +1^\circ.3$ ).

$C = \kappa W = 0.01286 \cdot 50.3 \cdot 100/50 = 1.3632$ .

$\log C = 0.13456$ .

#### Conductivity cell II.

*N*/10 potassium chloride solution.

Temperature 24°.90 C.

Frequency 2000 cycles.

Adjustment  $N = 100$   $Z = 50$   $\phi = 0^\circ$ .

Measurement  $Z = 58.0$  ( $\phi = +1^\circ.2$ ).

$C = \kappa W = 0.01286 \cdot 58.0 \cdot 100/50 = 1.4918$ .

$\log C = 0.17371$ .

The potassium chloride solution was prepared as described by *L. Michaelis*, "Praktikum der physikalischen Chemie (insbesondere der Kolloidchemie für Mediziner und Biologen)", 3rd Ed., Jul. Springer, Berlin 1926 (p. 145).

Potassium chloride (*pro analysi*, *Kahlbaum*) was ignited slightly and cooled in a desiccator; 7.44 g were dissolved in 1 l "conductivity water". The specific conductivity of the solution 0.01286 at 24°.90 C was found by interpolation between 0.01143 at 19°C and 0.01288 at 25°C. (These values were taken from *L. Michaelis*, *loc. cit.*).

The cell constant was checked before every series of experiments; the values given above were found to be constant during all experiments. (NB. no platinizing of the electrodes.)

#### Experiments *K 1*, *K 2*.

Experiment No.	Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 1</i>		10	3.64	24	I.	24°.90	2000	216.2
21—6—39								+1.0
<i>K 2</i>		15	3.54	137	II.	24°.90	2000	177.3
12—10—39								+1.0

In Tables *K 1—K 13*, the time *t* is given in seconds;  $\Delta\kappa$  is the change in specific conductivity in ohm<sup>-1</sup> cm<sup>-1</sup>.

<sup>1)</sup> For the performance of the measurements and the significance of the magnitudes *N*, *Z*,  $\phi$ , *C*,  $\kappa$ , and *W*, cf. § 42 b, p. 173.

Experiments K 1, K 2. Table K 1.

Table K 1.  
(cf. Figs. A 2 and A 3).

Experiment No. K 1						Experiment No. K 2		
$(t_1)$	$t_2$	$t_3$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	0	0	0	6.305	0.000	0	8.414	0.000
1,5	2	2	2	6.257	0.048	2	8.355	0.059
6	6	6	6	6.225	0.080	3	8.316	0.098
18	18	17	18	6.193	0.112	7	8.269	0.145
41	42	41	41	6.161	0.144	13	8.226	0.188
75	75	74	75	6.129	0.176	23	8.182	0.232
120	121	120	120	6.097	0.208	37	8.139	0.275
130	131	130	130	6.091	0.214	59	8.097	0.317
142	143	142	142	6.084	0.221	97	8.053	0.361
180	181	180	180	6.065	0.240	143	8.011	0.403
(191	192	191)	191	6.059	0.246	194	7.968	0.446
						240	7.585	0.829

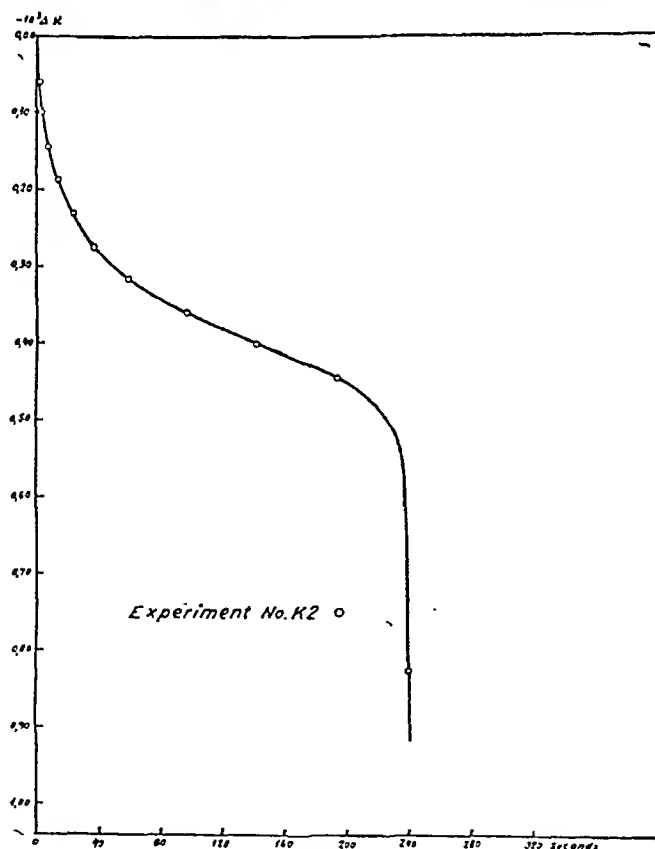


Fig. A 2.

The cataphoretic conductivity of blood sample crt. No. 15 (experiment No. K 2).  
 Ordinates:  $\Delta \kappa$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).  
 Abscissae: time in seconds.

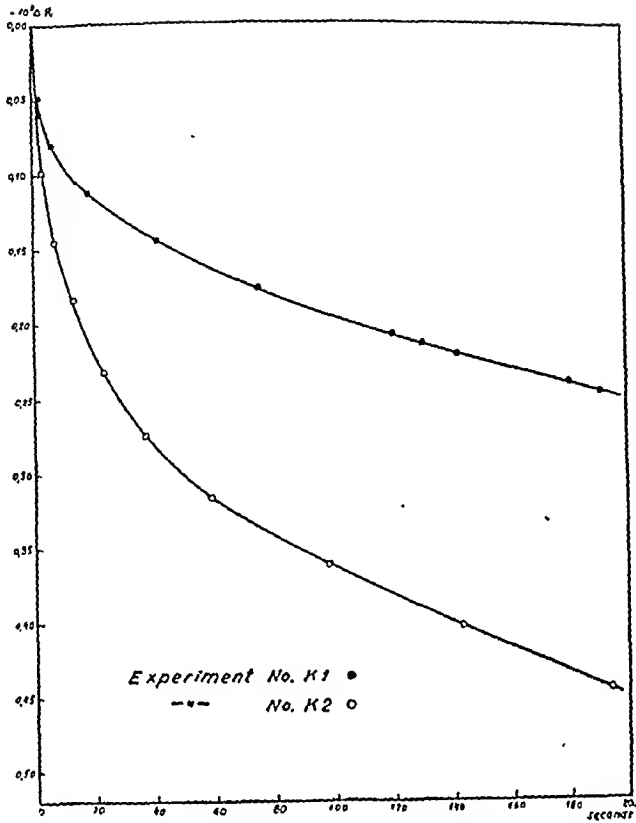
Experiments *K 1—K 5*.

Fig. A 3.

The cataphoretic conductivity of blood samples crt. Nos. 10 and 15 (experiments Nos. *K 1* and *K 2*).

Ordinates:  $\Delta \kappa$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).

Abscissae: time in seconds.

Experiment No.	Date	Blood sample crt. No.	Erythrocyte count in $\text{mill/mm}^3$	Sedimentation test in $\text{mm/hour}$ at $20^\circ\text{C}$ .	Conductivity cell No.	Temperature in $^\circ\text{C}$ .	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 3</i>	12-6-39	6	4.70	7	I.	$24^\circ.90$	2000	184.8 +1.3
<i>K 4</i>	20-10-39	19	4.77	16	II.	$24^\circ.90$	2000	207.3 +1.1
<i>K 5</i>	16-8-39	13	4.77	79	II.	$24^\circ.90$	2000	216.0 +1.2

Experiments K 3—K 5. Table K 2.

Table K 2.  
(cf. Fig. A 4).

Experiment No. K 3			Experiment No. K 4			Experiment No. K 5		
$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	7.377	0.000	0	7.196	0.000	0	6.907	0.000
3	7.345	0.032	2	7.138	0.058	1	6.834	0.073
8	7.307	0.070	4	7.105	0.091	2	6.795	0.112
19	7.271	0.106	8	7.072	0.124	4	6.755	0.152
30	7.256	0.121	13	7.040	0.156	6	6.715	0.192
47	7.241	0.136	24	7.007	0.189	8	6.677	0.230
58	7.234	0.143	38	6.975	0.221	10	6.639	0.268
70	7.228	0.149	58	6.944	0.252	14	6.601	0.306
98	7.220	0.157	88	6.914	0.282	22	6.563	0.344
			154	6.880	0.316	33	6.526	0.381
			225	6.849	0.347	80	6.465	0.442
						130	6.438	0.469
						190	6.418	0.489

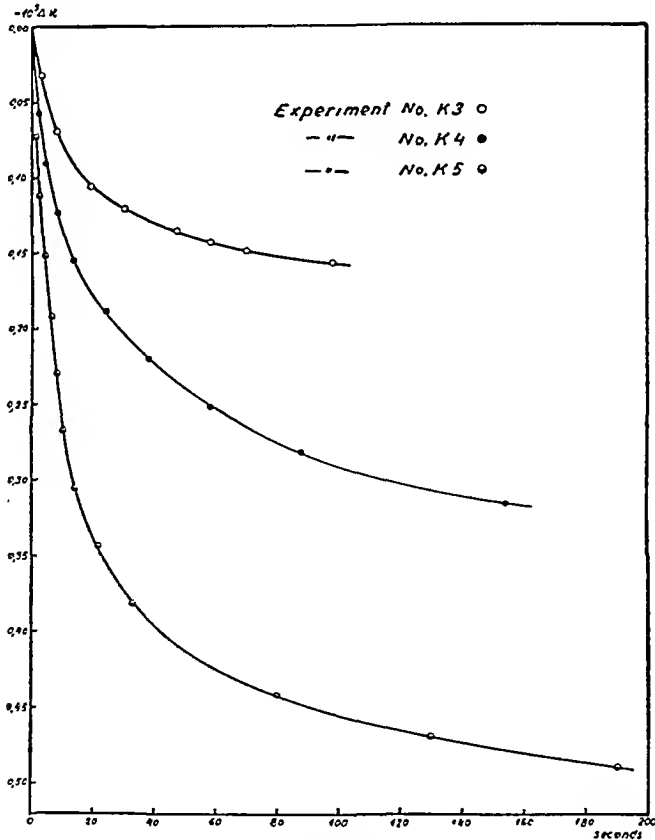


Fig. A 4.

The cataphoretic conductivity of blood samples crt. Nos. 6, 19 and 13 (experiments Nos. K 3, K 4 and K 5).

Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm $^{-1}$  cm $^{-1}$ ).

Abscissae: time in seconds.



Experiments K 6, K 7.

Experiment No.	Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
K 6	17-6-39	9	5.06	5	I.	24°.90	2000	148.0 +1.0
K 7	16-10-39	17	5.09	24	II.	24°.90	2000	202.2 +1.0

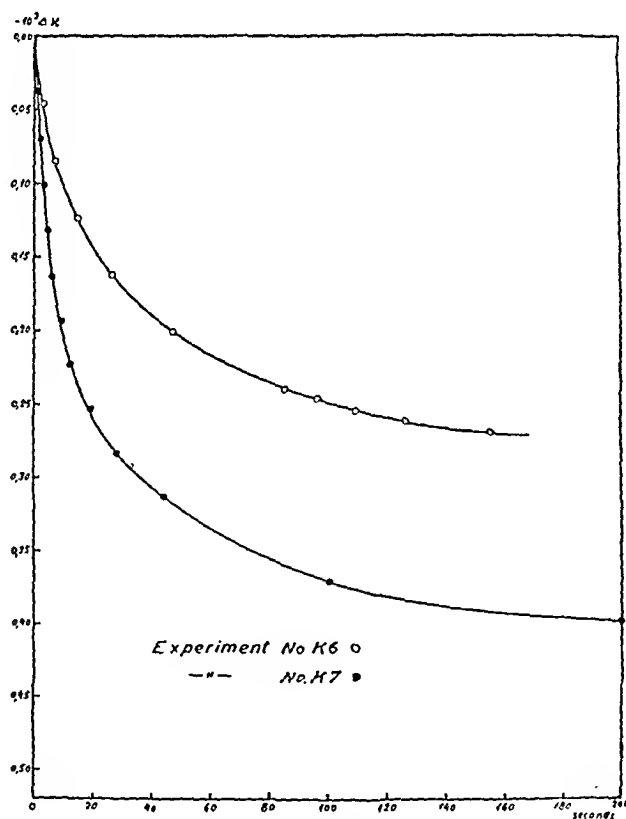


Fig. A 5.

The cataphoretic conductivity of blood samples crt. Nos. 9 and 17 (experiments Nos. K 6 and K 7).

Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm<sup>-1</sup> cm<sup>-1</sup>).

Abscissae: time in seconds.

Experiments *K 6*—*K 9*. Tables *K 3*, *K 4*.

*Table K 3.*  
(*cf.* Fig. A 5, p. 212).

Experiment No. <i>K 6</i>			Experiment No. <i>K 7</i>		
<i>t</i>	$10^3 \%$	$-10^3 \Delta\%$	<i>t</i>	$10^3 \%$	$-10^3 \Delta\%$
0	7.441	0.000	0	7.378	0.000
3	7.395	0.046	1	7.340	0.038
7	7.356	0.085	2	7.308	0.070
15	7.317	0.124	3.5	7.277	0.101
26	7.278	0.163	4.5	7.246	0.132
47	7.240	0.201	6	7.215	0.163
85	7.201	0.240	9	7.184	0.194
96	7.194	0.247	12.5	7.154	0.224
109	7.186	0.255	19	7.124	0.254
126	7.179	0.262	28	7.094	0.284
155	7.171	0.270	44	7.064	0.314
249	7.163	0.278	100	7.007	0.371
			200	6.979	0.399

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 8</i> 18—10—39	18	5.20	4	II.	24°.90	2000	219.0 +1.0
<i>K 9</i> 13—6—39	7	5.35	8	I.	24°.90	2000	184.6 +1.0

*Table K 4.*  
(*cf.* Fig. A 6, p. 214).

Experiment No. <i>K 8</i>			Experiment No. <i>K 9</i>		
<i>t</i>	$10^3 \%$	$-10^3 \Delta\%$	<i>t</i>	$10^3 \%$	$-10^3 \Delta\%$
0	6.812	0.000	0	7.385	0.000
1	6.750	0.062	0.5	7.301	0.084
3	6.690	0.122	1.5	7.262	0.123
5	6.660	0.152	4	7.223	0.162
9	6.630	0.182	11	7.186	0.199
20	6.601	0.211	25	7.148	0.237
48	6.572	0.240	45	7.111	0.274
100	6.549	0.263	81	7.074	0.311
133	6.543	0.269	161	7.038	0.347
165	6.537	0.275			
200	6.531	0.281			
300	6.529	0.283			

## Experiments K 8—K 11.

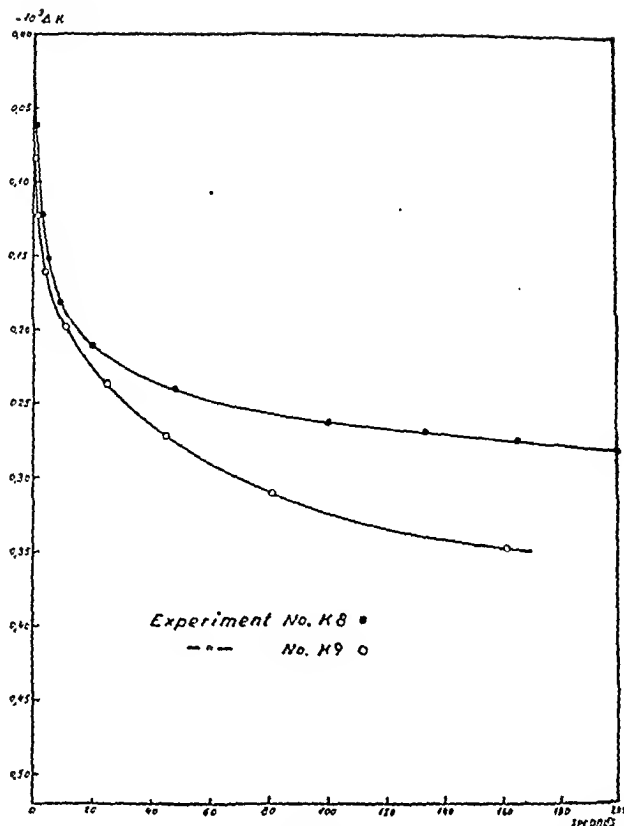


Fig. A 6.

The cataphoretic conductivity of blood samples crt. Nos. 18 and 7 (experiments Nos. K 8 and K 9).

Ordinates:  $\Delta\%$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).

Abscissae: time in seconds.

Experiment No.	Blood sample crt. No.	Erythrocyte count in $\text{mill/mm}^3$	Sedimentation test in $\text{mm/hour}$ at $20^\circ\text{C}$ .	Conductivity cell No.	Temperature in $^\circ\text{C}$ .	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
K 10 22-6-39	11	4.13	55 <sup>1)</sup>	I.	$24^\circ.90$	2000	144.0 +1.1
K 11 14-6-39	8	2.03	12	I.	$24^\circ.90$	2000	135.4 +1.2

<sup>1)</sup> Diffuse interface.

Experiments *K 10*, *K 11*. Table *K 5*.Table *K 5*.  
(cf. Fig. A 7).

Experiment No. <i>K 10</i>			Experiment No. <i>K 11</i>		
$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	9.467	0.000	0	10.068	0.000
3	9.398	0.069	6	9.918	0.150
8	9.331	0.136	11	9.852	0.216
15	9.266	0.201	26	9.788	0.280
29	9.203	0.264	58	9.723	0.345
61	9.142	0.325	81	9.698	0.370
84	9.115	0.352	110	9.691	0.387
128	9.079	0.388			
144	9.067	0.400			
162	9.055	0.412			
180	9.043	0.424			

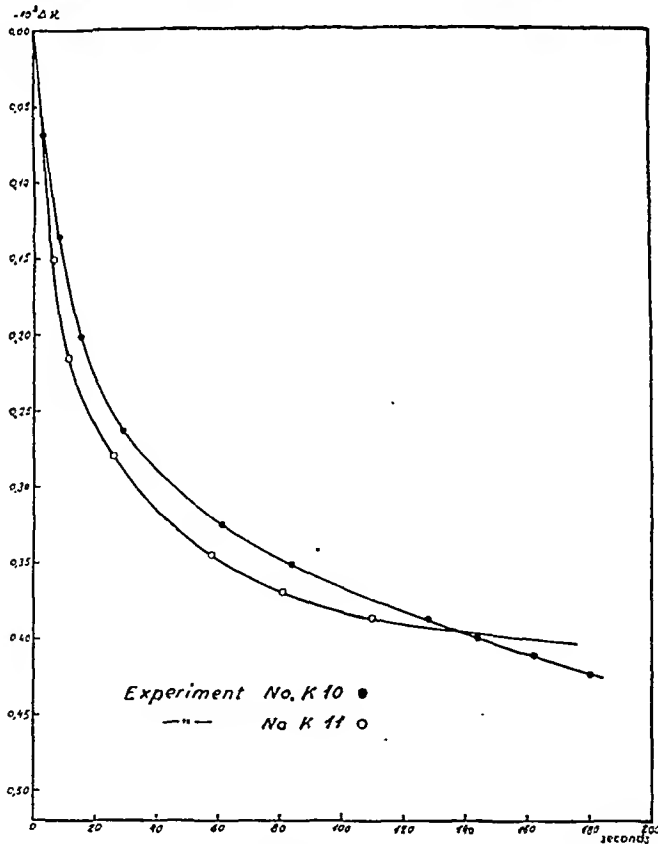


Fig. A 7.

The cataphoretic conductivity of blood samples crt. Nos. 11 and 8 (experiments Nos. *K 10* and *K 11*).

Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm<sup>-1</sup> cm<sup>-1</sup>).

Abscissae: time in seconds.

Experiments *K 3*, *K 12*, *K 13*. Table *K 6*.

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 3</i> 12-6-39	6	4.70	7	1.	24°.90	2000	184.8 +1.3
<i>K 12</i> 12-6-39	6 <sup>1)</sup>	3.85	9	1.	24°.90	2000	212.4 +1.3
<i>K 13</i> 12-6-39	6 <sup>2)</sup>	3.85	86	1.	24°.90	2000	212.0 +1.4

<sup>1)</sup> 45 cc whole blood+10 cc isotonic glucose solution.

<sup>2)</sup> 45 cc whole blood+10 cc isotonic glucose solution with 0.5% tylose.

Table *K 6*.  
(cf. Fig. *A 8*, p. 217).

Experiment No. <i>K 3</i>			Experiment No. <i>K 12</i>			Experiment No. <i>K 13</i>		
<i>t</i>	10 <sup>3</sup> $\kappa$	-10 <sup>3</sup> $\Delta\kappa$	<i>t</i>	10 <sup>3</sup> $\kappa$	-10 <sup>3</sup> $\Delta\kappa$	<i>t</i>	10 <sup>3</sup> $\kappa$	-10 <sup>3</sup> $\Delta\kappa$
0	7.377	0.000	0	6.418	0.000	0	6.430	0.000
3	7.345	0.032	2	6.386	0.032	1	6.363	0.067
8	7.307	0.070	6	6.351	0.067	2	6.330	0.100
19	7.271	0.106	14	6.318	0.100	3	6.299	0.131
30	7.256	0.121	33	6.288	0.130	5	6.269	0.161
47	7.241	0.136	73	6.257	0.161	9.5	6.237	0.193
58	7.234	0.143	159	6.226	0.194	24	6.190	0.240
70	7.228	0.149				30	6.178	0.252
98	7.220	0.157				37	6.166	0.264
						51	6.149	0.281
						141	6.070	0.360

Experiments K 3, K 12, K 16.

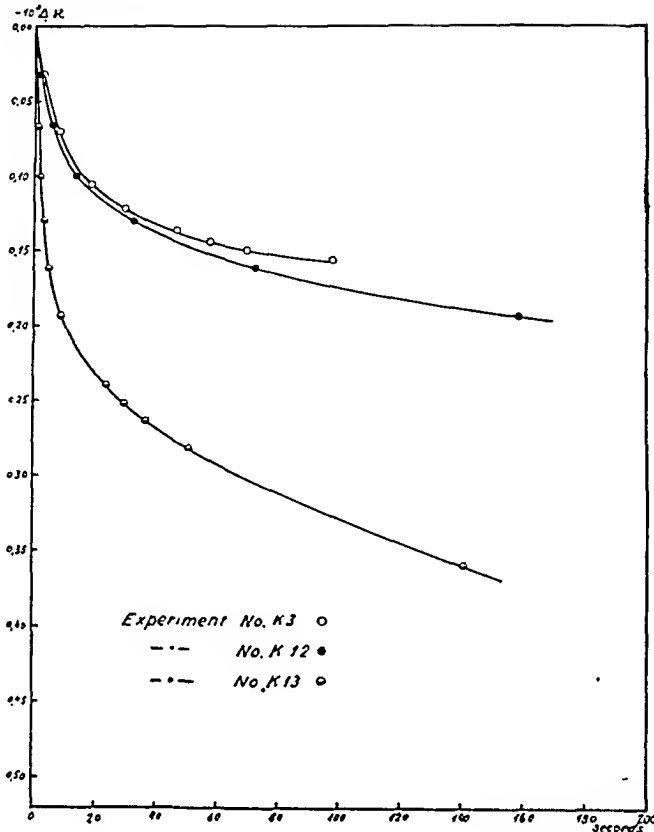


Fig. A 8.

The cataphoretic conductivity of the undilute blood sample crt. No. 6 (exp. No. K 3), after addition of isotonic glucose solution (exp. No. K 12) and after addition of isotonic glucose solution + tylose (exp. No. K 13).

Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm<sup>-1</sup> cm<sup>-1</sup>).

Abscissae: time in seconds.

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
K 14 11-9-39	14 <sup>1)</sup>	4.93	2	II.	24°.90	2000	224.7 +1.0
K 15 11-9-39	14 <sup>2)</sup>	4.93	0.2	II.	24°.90	2000	123.0 +1.5
K 16 11-9-39	14 <sup>3)</sup>	4.93	0.6	II.	24°.90	2000	129.0 +1.5

<sup>1)</sup> Blood type A.

<sup>2)</sup> 50 cc whole blood—5 cc plasma+5 cc 5% sodium chloride solution.

<sup>3)</sup> 50 cc whole blood—25 cc plasma+5 cc 5% sodium chloride solution+20 cc test serum type B; agglutinin titre 1 : 64.

Experiments *K 14*—*K 19*. Table *K 7*.Table *K 7*.  
(cf. Fig. A 9, p. 219).

Experiment No. <i>K 14</i>			Experiment No. <i>K 15</i>			Experiment No. <i>K 16</i>		
<i>t</i>	$10^3 \%$	$-10^3 \Delta \%$	<i>t</i>	$10^3 \%$	$-10^3 \Delta \%$	<i>t</i>	$10^3 \%$	$-10^3 \Delta \%$
0	6.639	0.000	0	12.128	0.000	0	11.564	0.000
1	6.603	0.036	30	12.128	0.000	1	11.546	0.018
2	6.573	0.064	100	12.128	0.000	2	11.529	0.035
4	6.544	0.095	200	12.128	0.000	3	11.510	0.054
6	6.514	0.125				4	11.493	0.071
8	6.485	0.154				5	11.476	0.088
12	6.457	0.182				6	11.458	0.106
16	6.429	0.210				7	11.440	0.124
21	6.401	0.238				8	11.423	0.141
26	6.373	0.266				10	11.405	0.159
34	6.345	0.294				13	11.388	0.176
100	6.246	0.393				23	11.370	0.194
200	6.212	0.427				60	11.353	0.211
						100	11.353	0.211
						200	11.353	0.211

Experiment No.	Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 17</i>		12	5.38	2	II.	24°.90	2000	234.3
11—8—39								+1.0
<i>K 18</i>		12 <sup>1)</sup>	2.69	19	II.	24°.90	2000	144.0
11—8—39								+1.0
<i>K 19</i>		12 <sup>2)</sup>	1.35	35	II.	24°.90	2000	115.7
11—8—39								+1.2

<sup>1)</sup> 25 cc whole blood+25 cc plasma.<sup>2)</sup> 25 cc 1)+25 cc plasma.

Experiments K 15—K 19. Table K 8.

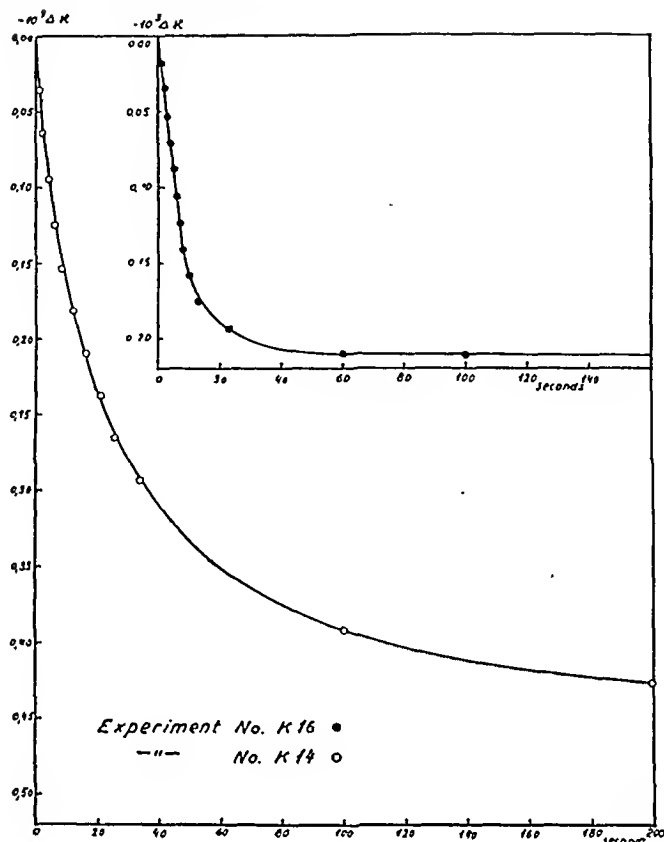


Fig. A 9.

The cataphoretic conductivity of blood sample crt. No. 14 as whole blood (exp. No. K 14) after addition of hypertonic sodium chloride solution (exp. No. K 15), and after addition of salt solution + an agglutinating test serum (exp. No. K 16).

Ordinates:  $\Delta \kappa$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).

Abscissae: time in seconds.

Table K 8.

(cf. Fig. A 10, p. 220).

Experiment No. K 17			Experiment No. K 18			Experiment No. K 19		
$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$	$t$	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	6.367	0.000	0	10.360	0.000	0	12.894	0.000
2	6.340	0.027	3	10.221	0.139	2	12.783	0.111
4	6.305	0.062	6	10.131	0.229	6	12.744	0.150
6	6.272	0.095	18	10.046	0.314	15	12.708	0.186
8	6.238	0.129	48	9.962	0.398	31	12.674	0.220
11	6.204	0.163	125	9.876	0.484	49	12.653	0.241
15	6.171	0.196				80	12.637	0.257
19	6.139	0.228				132	12.621	0.273
25	6.106	0.261						
38	6.074	0.293						
60	6.042	0.325						
190	5.975	0.392						



Experiments K 6, K 17—K 21.

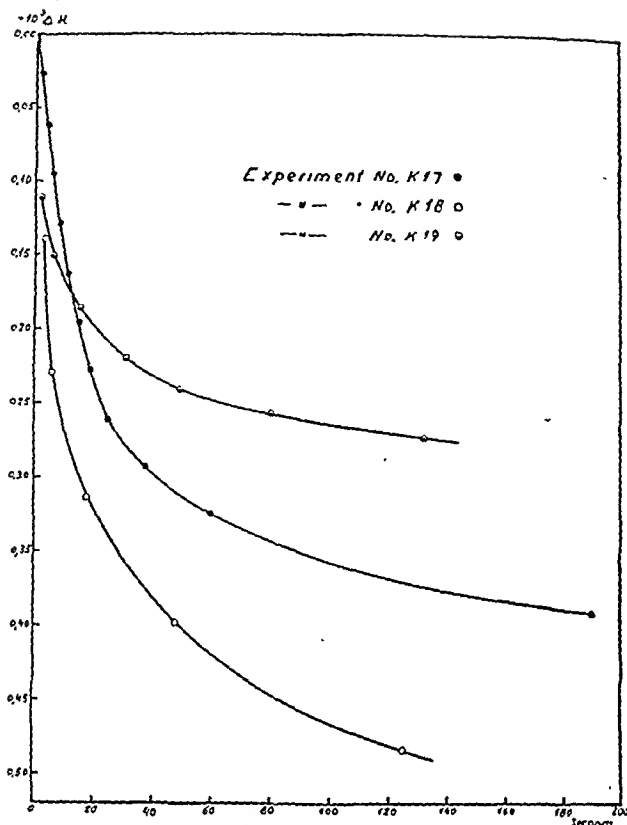


Fig. A 10.

The cataphoretic conductivity of blood sample crt. No. 12 as whole blood (exp. No. K 17), blood-plasma dilution 1 : 2 (exp. No. K 18), and blood-plasma dilution 1 : 4 (exp. No. K 19).

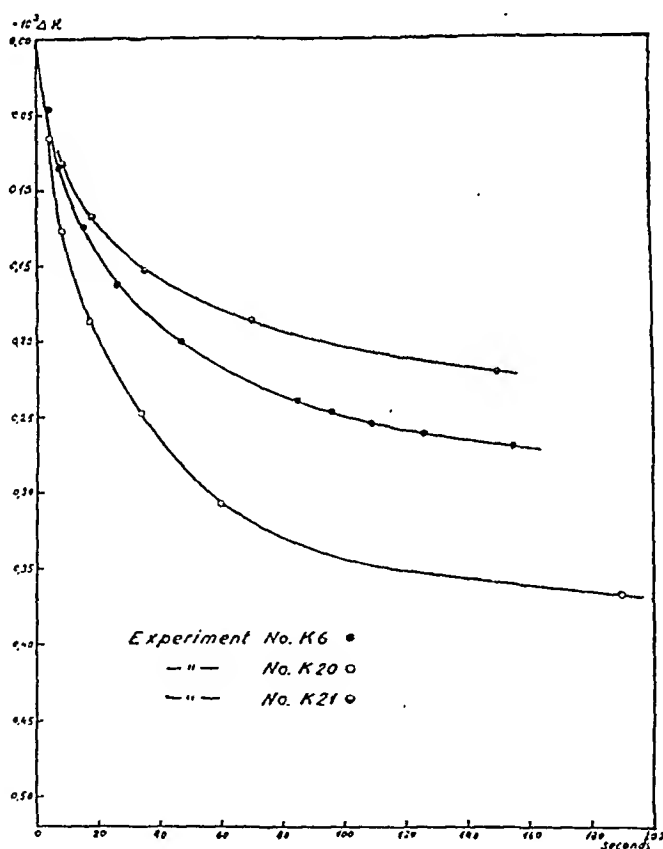
Ordinates:  $\Delta\%$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).

Abscissae: time in seconds.

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in $\text{mill/mm}^3$	Sedimentation test in $\text{mm/hour}$ at $20^\circ\text{C}$ .	Conductivity cell No.	Temperature in $^\circ\text{C}$ .	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
K 20 17-6-39	9	5.06	5	I.	$37^\circ.60$	2000	148.0 +1.1
K 6 17-6-39	9	5.06	5	I.	$24^\circ.90$	2000	183.2 +1.1
K 21 17-6-39	9	5.06	5	I.	$11^\circ.20$	2000	249.6 +1.0

Experiments *K 6*, *K 20*, *K 21*. Table *K 9*.Table *K 9*.  
(cf. Fig. *A 11*).

Experiment No. <i>K 20</i>			Experiment No. <i>K 6</i>			Experiment No. <i>K 21</i>		
<i>t</i>	$10^3 \kappa$	$-10^3 \Delta \kappa$	<i>t</i>	$10^3 \kappa$	$-10^3 \Delta \kappa$	<i>t</i>	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	9.211	0.000	0	7.441	0.000	0	5.462	0.000
4	9.146	0.065	3	7.395	0.046	8	5.379	0.083
8	9.084	0.127	7	7.356	0.085	18	5.344	0.118
17	9.024	0.187	15	7.317	0.124	35	5.309	0.153
34	8.963	0.248	26	7.278	0.163	70	5.275	0.187
60	8.903	0.308	47	7.240	0.201	145	5.241	0.221
190	8.843	0.368	85	7.201	0.240			
			96	7.194	0.247			
			109	7.186	0.255			
			126	7.179	0.262			
			155	7.171	0.270			
			249	7.163	0.278			

Fig. *A 11*.

The cataphoretic conductivity of blood sample crt. No. 9 at 37°,60 C. (exp. No. *K 20*), at 24°,90 C. (exp. No. *K 6*), and at 11°,20 C. (exp. No. *K 21*).  
 Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm<sup>-1</sup> cm<sup>-1</sup>).  
 Abscissae: time in seconds.

## Experiments K 22—K 24.

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
K 22 14—10—39	16	5.00	2	II.	24°.90	2000	224.4 +1.1
K 23 20—10—39	20	5.40	2	II.	24°.90	2000	236.1 +1.2
K 24 20—10—39	20 <sup>1)</sup>	2.70	18	II.	24°.90	2000	144.9 +1.3

<sup>1)</sup> 25 cc whole blood + 25 cc plasma.

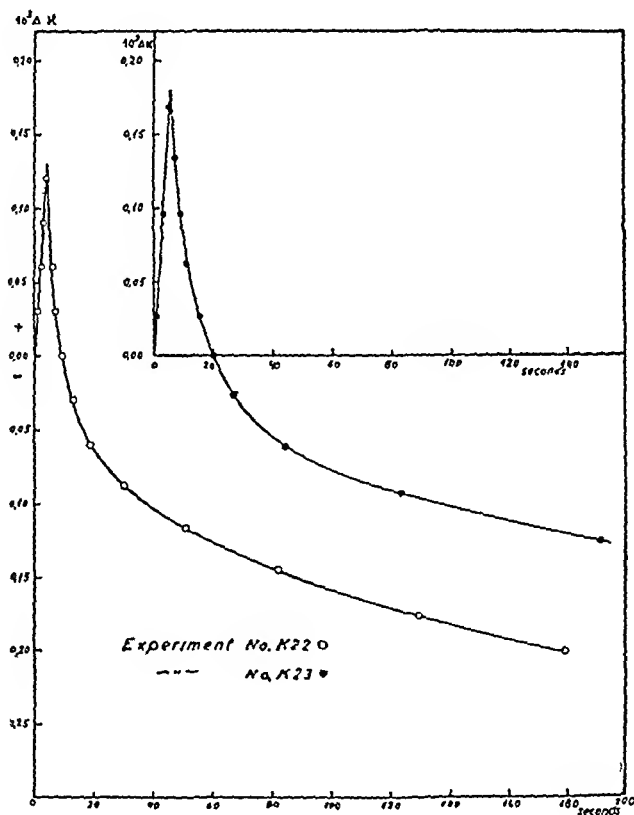


Fig. A 12.

The cataphoretic conductivity of blood samples crt. No. 16 (exp. No. K 22) and crt. No. 20 (exp. No. K 23).

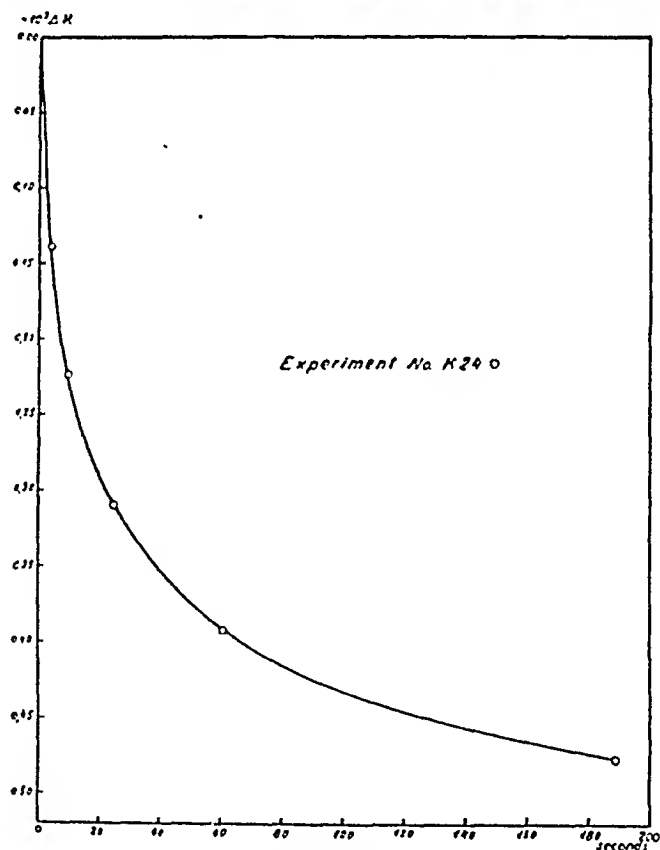
Ordinates:  $\Delta \kappa$  change in specific conductivity ( $\text{ohm}^{-1} \text{cm}^{-1}$ ).

Abscissae: time in seconds.

Experiments *K* 22—*K* 24. Table *K* 12.

Table *K* 10.  
(cf. Figs. *A* 12, p. 222 and *A* 13).

Experiment No. <i>K</i> 22			Experiment No. <i>K</i> 23			Experiment No. <i>K</i> 24		
<i>t</i>	$10^3 \kappa$	$10^3 \Delta \kappa$	<i>t</i>	$10^3 \kappa$	$10^3 \Delta \kappa$	<i>t</i>	$10^3 \kappa$	$-10^3 \Delta \kappa$
0	6.648	+0.000	0	6.318	+0.000	0	10.295	0.000
1	6.678	+0.030	1	6.345	+0.027	4	10.156	0.139
2	6.708	+0.060	3	6.415	+0.097	10	10.071	0.224
3	6.738	+0.090	5	6.487	+0.169	25	9.985	0.310
4	6.769	+0.121	7	6.451	+0.133	61	9.902	0.393
6	6.708	+0.060	9	6.415	+0.097	189	9.818	0.477
7	6.678	+0.030	11	6.381	+0.063			
9	6.648	0.000	15	6.345	+0.027			
13	6.619	-0.029	20	6.318	0.000			
19	6.589	-0.059	27	6.292	-0.026			
30	6.560	-0.088	44	6.257	-0.061			
51	6.531	-0.117	83	6.225	-0.093			
82	6.503	-0.145	191	6.191	-0.127			
129	6.475	-0.173						
179	6.447	-0.201						

Fig. *A* 13.

The cathaphoretic conductivity of blood sample crt. No. 20, diluted with equal parts of plasma (exp. No. *K* 24).

Ordinates:  $\Delta \kappa$  change in specific conductivity (ohm<sup>-1</sup> cm<sup>-1</sup>).

Abscissae: time in seconds.

Experiments *K 11*, *K 25*—*K 29*. Tables *K 11*, *K 12*.

Experiment No. Date	Blood sample crt. No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 17</i> and <i>K 25</i> — <i>29</i> 11—8—39	12	5.38	2	II.	24°.90	2000	234.3 +1.0

Table *K 11*.

First experiment at the transition from to.		<i>K 25</i> 338 0	<i>K 17</i> 266 0	<i>K 26</i> 204 0	} rot./min.
10 <sup>3</sup> %	—10 <sup>3</sup> Δ%	<i>t</i>	<i>t</i>	<i>t</i>	
6.367	0.000	0	0		
6.340	0.027	2	2		
6.305	0.062	4	4		
6.272	0.095	6	6	0	0.000
6.238	0.129	8	8	2	0.034
6.204	0.163	12	11	5	0.068
6.171	0.196	16	15	9	0.101
6.139	0.228	20	19	13	0.133
6.106	0.261	26	25	20	0.166
6.074	0.293	39	38	33	0.198
6.042	0.325	61	60	53	0.230
5.975	0.392		190	185	0.297

Table *K 12*.

Second experiment at the transition from to		<i>K 27</i> 266 100	<i>K 28</i> 266 164	<i>K 29</i> 266 204	} rot./min.
10 <sup>3</sup> %	—10 <sup>3</sup> Δ%	<i>t</i>	<i>t</i>	<i>t</i>	
6.367	0.000	0	0	0	
6.272	0.095			6	
6.042	0.325	3	7		

*Ad K 27 and K 28*: After 3 and 7 sec, respectively, the effect continued, however, it was not measured any further.

*Ad K 29*: The effect ceased after 6 sec, since the conductivity became again constant. *K 26* was carried out in subsequence of *K 29*, only stirring was stopped, and the new constant conductivity was regarded as origin.

*Ad K 26*: If the curve of *K 26* is drawn with (—10<sup>3</sup> Δ% = 0.095, and *t* = 6 sec) as origin, the curve of *K 26* overlaps completely with the last part of *K 17*.

Experiments *K 4*, *K 30*. Table *K 13*.

Experiment No. Date	Blood sample crt.No.	Erythrocyte count in mill/mm <sup>3</sup>	Sedimentation test in mm/hour at 20°C.	Conductivity cell No.	Temperature in °C.	Frequency in cycles	Initial impedance in ohms and phase angle in degrees
<i>K 4</i> 20-10-39	19	4.77	16	II.	24° 90	2000	207.3 +1.1
<i>K 30</i> 20-10-39	19 <sup>1)</sup>	4.77	15	II.	24° 90	2000	207.0 +1.1

<sup>1)</sup> Blood sample saturated with alveolar air.Table *K 13*.

Experiment No. <i>K 4</i>			Experiment No. <i>K 30</i>		
<i>t</i>	10 <sup>3</sup> $\alpha$	-10 <sup>3</sup> $\Delta\alpha$	<i>t</i>	10 <sup>3</sup> $\alpha$	-10 <sup>3</sup> $\Delta\alpha$
0	7.196	0.000	0	7.207	0.000
2	7.138	0.058	2	7.148	0.059
4	7.105	0.091	4	7.115	0.092
8	7.072	0.124	8	7.082	0.125
13	7.040	0.156	14	7.049	0.158
24	7.007	0.189	24	7.017	0.190
38	6.975	0.221	39	6.985	0.222
58	6.944	0.252	60	6.953	0.254
88	6.914	0.282	91	6.922	0.285
154	6.880	0.316	159	6.890	0.317
225	6.849	0.347			

The curve of exp. No. *K 30* overlaps practically that of exp. No. *K 4* shown in Fig. *A 4*, p. 211.

C. INVESTIGATIONS CONCERNING N. RASHEVSKY'S METABOLISM  
HYPOTHESIS.

Composition of the solutions.

Solution	Substance	Quantity in grams	H <sub>2</sub> O dist.	Molarity <sup>1)</sup>	Table	Page
Potassium fluoride	KF, 2H <sub>2</sub> O	10.23	ad 50 g	0.027	S. 1	227
Potassium cyanide	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O KCN	10 2	ad 50 g	0.0077	S. 2	229
Sodium azide.....	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O NaN <sub>3</sub>	10 0.26	ad 50 g	0.001	S. 3	230
Potassium mono- iodo acetate I ...	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O JCH <sub>2</sub> COOK	10 0.089	ad 50 g	0.0001	S. 5	232
Potassium mono- iodo acetate II...	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O JCH <sub>2</sub> COOK	10 0.178	ad 50 g	0.0002	S. 5	232
Glucose .....	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O C <sub>6</sub> H <sub>12</sub> O <sub>6</sub>	10 8	ad 50 g	increase 0.1%	S. 6	233
Fumaric acid .....	K <sub>2</sub> C <sub>2</sub> O <sub>4</sub> , H <sub>2</sub> O C <sub>4</sub> O <sub>4</sub> H <sub>4</sub>	10 0.464	ad 50 g	0.001	S. 7	234

Oxalate blood saturated with carbon monoxide (Kitchen gas) .	S. 4	231
Oxalate blood saturated with hydrogen sulfide .....	S. 8	235

<sup>1)</sup> Molarity with respect to the salt after addition of 0.1 cc of the solution to 8 cc blood.

Blood samples crt. Nos. 25—36.

Table S 1.

Comparison of the sedimentation tests of oxalate blood and fluoride blood.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B		
						oxa- late blood	fluor- ide blood			
									mm/1 hour at 20°C	
									A	B
25. 625 9-2-39	♀ Chronic bronchitis	F. H. <sup>1)</sup> Dep. E I No. 3101	71	4.01	0.90	65 <sup>3)</sup>	25 (5-34 <sup>4)</sup> )	40		
26. 615 9-2-39	♂ Pott's disease	F. H. . Dep. E. I No. 4894	52	—	—	40 <sup>3)</sup>	5 (5-22 <sup>4)</sup> )	35		
27. 690 9-2-39	♀ Cancer of uterus	R. St. <sup>2)</sup> No. 19745	35	1.92	0.91	19 <sup>3)</sup>	coag.	—		
28. 682 10-2-39	♀ Cancer of the breast	R. St. No. 19788	79	4.57	0.85	16	3 (3-7 <sup>4)</sup> )	13		
29. 653 10-2-39	♂ Colitis	F. H. Dep. E I No. 5158	93	5.26	0.89	3	1	2		
30. 697 10-2-39	♀ Cancer of rectum	R. St. No. 19751	62	3.30	0.94	42 <sup>3)</sup>	2 (2-13 <sup>4)</sup> )	40		
31. 698 10-2-39	♂ Cervical eczema	F. H. Dermat. Dep. No. 70568	99	4.33	1.14	5	2	3		
32. 776 11-2-39	♀ Arthritis deformans	F. H. Dep. E I No. 4249	77	3.70	1.04	44 <sup>3)</sup>	16 <sup>3)</sup>	28		
33. 786 11-2-39	♂ Arthrit. def. of spine	F. H. Dep. E I No. 1544	—	—	—	16	4	12		
34. 781 11-2-39	♂ Simple Anaemia	F. H. Dep. E I No. 5133	72	—	—	85	68	17		
35. 710 14-2-39	♀ Influenza	F. H. Dep. E No. 402F	88	—	—	4	2 (2-3 <sup>4)</sup> )	2		
36. 720 14-2-39	♀ Chilblain	F. H. Dermat. Dep. No. 79280	88	4.57	0.97	4	2	2		

<sup>1)</sup> F.H. = Finsen Hospital.

<sup>2)</sup> R.St. = Radium Station.

<sup>3)</sup> Diffuse interface.

<sup>4)</sup> Bloody, diffuse.



Blood samples crt. Nos. 37-47.

Table S 1 (Contin.)

Comparison of the sedimentation tests of oxalate blood and fluoride blood.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B
						oxa- late blood	fluor- ide blood	
						mm/1 hour at 20°C		
						A	B	
37. 740 14-2-39	♀ Bronchitis	F. H. <sup>1)</sup> Dep. E I No. 5161	85	—	—	20	3 (3-18 <sup>4</sup> )	17
38. 745 15-2-39	♀ Grave's disease	F. H. Dep. E I No. 5178	71	—	—	7	7	0
39. 880 15-2-39	♀ Diabetes mellitus	F. H. Dep. E I No. 4306	89	—	—	5	3	2
40. 889 15-2-39	♂ Ischias	F. H. Dep. E I No. 5190	111	—	—	2	2	0
41. 455 16-2-39	♀ Anaemia	F. H. Dermat. Dep. No. 73083	72	—	—	7	4 (4-12 <sup>4</sup> )	3
42. 435 16-2-39	♀ Rheuma- toid ar- thritis	F. H. Dep. E I No. 3913	85	4.58	0.92	12	3	9
43. 500 16-2-39	♀ Cervical adenitis	F. H. Dep. E I No. 3820	81	4.56	0.89	4	2	2
44. 450 16-2-39	♀ Cervical adenitis	F. H. Surgical Dep. No. 15423	74	3.88	0.94	41 <sup>3)</sup>	31 <sup>3)</sup>	10
45. 445 16-2-39	♀ Prurigo	F. H. Dermat. Dep. No. 79121	93	3.87	1.20	11 <sup>3)</sup>	coag.	—
46. 440 16-2-39	♀ Cancer of the orbit	R. St. <sup>2)</sup> No. 12722	76	4.50	0.85	7	3 (3-7 <sup>4</sup> )	4
47. 421 17-2-39	♂ Fissure in-ano	F. H. Dep. E I No. 5183	90	4.40	1.02	7	3	4

<sup>1)</sup> F. H. = Finsen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

<sup>4)</sup> Bloody, diffuse.

Blood samples crt. Nos. 48—57.

Table S 2.

Comparison of the sedimentation tests of oxalate blood and cyanide blood.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B
						oxa- late blood	eyan- ide blood	
mm/1 hour at 20°C								
A	B							
48. 794 27-2-39	♀ Rheum- atoid arthritis	F. H. <sup>1)</sup> Dep. E I No. 4249	—	—	—	37 <sup>3)</sup>	37 <sup>3)</sup>	0
49. 27-2-39	♀ Furuneu- losis	F. H. Dermat. Dep. No. 79675	90	4.30	1.04	18 <sup>3)</sup>	19 <sup>3)</sup>	—1
50. 737 28-2-39	♀ Mental Depress- ion	F. H. Dep. E I No. 5262	81	—	—	5	6	—1
51. 726 28-2-39	♀ Rheum- atoid arthritis	F. H. Dep. E I No. 5252	—	—	—	44 <sup>3)</sup>	48 <sup>3)</sup>	—4
52. 848 28-2-39	♀ Nervous disease	F. H. Dep. E I No. 5265	82	—	—	8	9	—1
53. 788 28-2-39	♀ Earlier syphilis	F. H. Dep. E I No. 5233	87	—	—	5	5	0
54. 721 28-2-39	♀ Vitamin deficiency	F. H. Dep. E I No. 5155	—	—	—	8	8	0
55. 896 1-3-39	♀ Melanotic cancer of leg	R. St. <sup>2)</sup> No. 18777	74	—	—	43 <sup>3)</sup>	45 <sup>3)</sup>	—2
56. 856 1-3-39	♂ Cancer of nose	R. St. No. 9308	82	3.99	1.02	25 <sup>3)</sup>	25 <sup>3)</sup>	0
57. 881 1-3-39	♀ Cancer of uterus	R. St. No. 19928	88	—	—	10	11	—1

<sup>1)</sup> F. H. = Finsen Hospital.<sup>2)</sup> R. St. = Radium Station.<sup>3)</sup> Diffuse interface.

Blood samples crt. Nos. 58—67.

Table S 3.

Comparison of the sedimentation tests of oxalate blood and sodium azide blood.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B		
						oxa- late blood	sodium azide blood			
									mm/1 hour at 20°C	
									A	B
58. 526 10-3-39	♀ Cancer of rectum	R. St. <sup>2)</sup> No. 18107	70	—	—	16	14	2		
59. 543 10-3-39	♀ Tumour of the breast	R. St. No. 19932	60	—	—	26 <sup>3)</sup>	28 <sup>3)</sup>	-2		
60. 533 10-3-39	♂ Pustulous eczema	F. H. <sup>1)</sup> Dermat. Dep. No. 80050	82	3.73	1.09	30 <sup>3)</sup>	25 <sup>3)</sup>	5		
61. 511 10-3-39	♀ Cancer of cervix uteri	R. St. No. 19738	59	—	—	42 <sup>3)</sup>	37 <sup>3)</sup>	5		
62. 521 10-3-39	♂ Cancer of auricle	R. St. No. 17807	67	—	—	19 <sup>3)</sup>	19 <sup>3)</sup>	0		
63. 541 10-3-39	♂ Tumour of palate	R. St. No. 18123	82	—	—	5	6	-1		
64. 546 10-3-39	♀ Cancer of maxilla	R. St. No. 12722	78	—	—	19	19	0		
65. 538 10-3-39	♀ Polypus uteri	R. St. No. 17146	81	—	—	8	8	0		
66. 635 10-3-39	♀ Choroi- ditiis	F. H. Ophtalm. Dep. No. 3650	82	—	—	9	11	-2		
67. 586 11-3-39	♀ Dys- pepsia	F. H. Dep. E I No. 5323	86	—	—	11	13	-2		

<sup>1)</sup> F. H. = Finsen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

Blood samples crt. Nos. 68—75.

Table S 4.

Comparison of the sedimentation tests of oxalate blood and blood saturated with carbon monoxide.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B
						oxa- late blood	carbon monox- ide blood	
						mm/1 hour at 20°C		
						A	B	
68. 514 22—2—39	♀ Rheum- atoid arthritis	F. H. <sup>1)</sup> Dep. E I No. 4091	68	3.76	0.91	71	70	1
69. 524 22—2—39	♀ Asthenia	F. H. Dep. E I No. 5223	80	3.90	1.03	18	18	0
70. 519 22—2—39	♀ Grave's disease	F. H. Dep. E I No. 5004	87	4.92	0.89	3—5 <sup>5)</sup>	3—5 <sup>5)</sup>	0
71. 22—2—39	♂ Hodg- kin's disease	R. St. <sup>2)</sup> No. 19335	49	3.36	0.73	50.64 <sup>4)</sup>	50—72 <sup>4)</sup>	—8
72. 22—2—39	♀ Cancer of cervix uteri	R. St. No. 19815	82	3.78	1.08	3	3	0
73. 22—2—39	♂ Rheuma- toid ar- thritis	F. H. Dep. E I No. 4438	72	4.76	0.77	18 <sup>3)</sup>	18 <sup>3)</sup>	0
74. 22—2—39	♂ Cancer of tonsil	R. St. No. 18668	98	5.17	0.95	3	3	0
75. 22—2—39	♂ Diabetes mellitus	F. H. Dep. E I No. 5221	98	—	—	10	11	—1

<sup>1)</sup> F. H. = Finsen Hospital

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

<sup>4)</sup> Bloody, diffuse.

<sup>5)</sup> Slightly diffuse.

Blood samples crt. Nos. 76-85.

Table S. 5.

Comparison of the sedimentation tests of oxalate blood and potassium moniodo acetate blood.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of			Diff. between sedimentation test of A and B	
						oxa- late blood	potassium monoiodo acetate blood			
							I.	II.		
							mm/1 hour at 20°C			
A	B	C								
76. 624 29-3-39	♀ Tumour of ovary	R. St. <sup>2)</sup> No. 20066	53	—		24 <sup>3)</sup>	25 <sup>3)</sup>	24 <sup>3)</sup>	B -1	C 0
77. 629 29-3-39	♀ Cancer of the uterus	R. St. No. 20016	52	—	—	86 <sup>3)</sup>	70 <sup>3)</sup>	86 <sup>3)</sup>	16	0
78. 619 29-3-39	♀ Cancer of cervix uteri	R. St. No. 19902	60	3.66	0.82	20	19	19	1	1
79. 638 29-3-39	♀ Stenocar- dia Nerv- ousness	F. H. <sup>1)</sup> Dep. E I No. 5470	85	—	—	11	11	11	0	0
80. 612 29-3-39	♀ Arthritis def. of kneejoint	F. H. Dep. E I No. 5466	90	—	—	14	12	14	2	0
81. 754 31-3-39	♂ Cancer of the lung	R. St. No. 19591	82	5.09	0.80	8	8	8	0	0
82. 774 31-3-39	♀ Cancer of uterus	R. St. No. 17473	59	—	—	93	90	103	3	-10
83. 759 31-3-39	♂ Hodg- kin's disease	R. St. No. 19335	55	3.17	0.87	85 <sup>3)</sup>	82 <sup>3)</sup>	75 <sup>3)</sup>	7	10
84. 772 31-3-39	♀ Angina	F. H. Dep. E I No. 295F R. St.	88	—	—	7	7	7	0	0
85. 769 31-3-39	♀ Cancer of the breast	No. 14950	109	5.08	1.07	18	18	19	0	-1

<sup>1)</sup> F. H. = Finsen Hospital.<sup>2)</sup> R. St. = Radium Station.<sup>3)</sup> Diffuse interface.

Blood samples crt. Nos. 86—95.

Table S. 6.  
Comparison of the sedimentation tests of oxalate blood  
and oxalate blood + glucose.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B		
						oxa- late blood	glu- cose blood			
									mm/1 hour at 20°C	
									A	B
86. 526 25-3-39	♂ Hodg- kin's disease	R. St. <sup>2)</sup> No. 19910	81	3.81	1.06	48 <sup>3)</sup>	48 <sup>3)</sup>	0		
87. 521 25-3-39	♀ Cancer of cervix uteri	R. St. No. 20032	75	3.71	1.00	27 <sup>3)</sup>	28 <sup>3)</sup>	-1		
88. 511 25-3-39	♂ Leu- kaemia	R. St. No. 16329	40	1.69	1.17	35 <sup>3)</sup>	30 <sup>3)</sup>	5		
89. 581 25-3-39	♂ Arthritis deformans	F. H. <sup>1)</sup> Dep. E I No. 5422	97	—	—	8	7	1		
90. 566 25-3-39	♀ Observ.	F. H. Dep. E I No. 296F	78	—	—	19	11	8		
91. 509 27-3-39	♀ Hodg- kin's disease	R. St. No. 19811	69	3.97	0.87	23	20	3		
92. 504 27-3-39	♀ Abdomin- al tumour	R. St. No. 19880	72	3.85	0.94	65 <sup>3)</sup>	38 <sup>3)</sup>	27		
93. 534 27-3-39	♀ Cancer of uterus	R. St. No. 20014	49	2.82	0.88	40 <sup>3)</sup>	40 <sup>3)</sup>	0		
94. 529 27-3-39	♀ Cancer of uterus	R. St. No. 13492	40	—	—	126 <sup>3)</sup>	118 <sup>3)</sup>	8		
95. 524 27-3-39	♀ Cancer of cervix uteri	R. St. No. 19692	56	—	—	35 <sup>3)</sup>	29 <sup>3)</sup>	6		

<sup>1)</sup> F. H. = Finsen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.

Blood samples *crt.* Nos. 96-106.

Table S. 7.

Comparison of the sedimentation tests of oxalate blood and oxalate blood+fumaric acid.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B
						oxa- late blood	fumar- acid blood	
						mm/1 hour at 20°C		
						A	B	
96. 467 8-3-39	♂ Tubercu- losis of kidney	F. H. <sup>1)</sup> Surgical Dep. No. 2600	91	—	—	9	10	-1
97. 472 8-3-39	♂ Tubercu- losis of foot	F. H. Surgical Dep. A No. 14513	56	—	—	75 <sup>2)</sup>	75 <sup>2)</sup>	0
98. 482 8-3-39	♂ Tumour of the lung	R. St. <sup>2)</sup> No. 19591	75	4.25	0.88	44 <sup>2)</sup>	38 <sup>2)</sup>	6
99. 492 8-3-39	♀ Cancer of cervix uteri	R. St. No. 19657	57	3.15	0.94	33 <sup>2)</sup>	32 <sup>2)</sup>	1
100. 462 8-3-39	♂ Tubercu- losis of the hip	F. H. Surgical Dep. A No. 12131	40	2.41	0.89	149	151	-2
101. 457 8-3-39	♂ Pott's disease	F. H. Surgical Dep. A No. 12103	55	3.00	0.70	160	160	0
102. 487 8-3-39	♀ Hodg- kin's disease	R. St. No. 18986	70	4.32	0.81	42 <sup>2)</sup>	35 <sup>2)</sup>	7
103. 567 9-3-39	♂ Arthritis deformans	F. H. Dep. E I No. 5302	99	—	—	5	9	-4
104. 478 9-3-39	♀ Cancer of uterus	R. St. No. 19979	34	2.37	0.72	14 <sup>2)</sup>	21 <sup>2)</sup>	-7
105. 473 9-3-39	♂ Eczema Prurigo	F. H. Dermat. Dep. No. 71091	85	—	—	6	7	-1
106. 505 9-3-39	♀ Obs. for cancer of the stomach	F. H. Dep. E I No. 5296	82	3.99	1.02	33 <sup>2)</sup>	49 <sup>2)</sup>	-16

<sup>1)</sup> F. H. = Finsen Hospital.<sup>2)</sup> R. St. = Radium Station.<sup>3)</sup> Diffuse interface.

Blood samples crt. Nos. 107—112.

Table S. 8.

Comparison of the sedimentation tests of oxalate blood  
and oxalate blood+hydrogen sulfide.

Blood sample Crt. No., No., Date	Sex Clinical Diagnosis	Hospital Dep. Case Report No.	Haemoglobin (Haldane) in per cent	Erythrocyte count in mm <sup>3</sup>	Colour index	Sediment- ation test of		Diff. between sedimentation test of A and B
						oxa- late blood	hydr. sulfide blood	
mm/1 hour at 20°C								
A	B							
107. 618 14-3-39	♀ Cancer of uterus	R. St. <sup>2)</sup> No. 19781	69	3.73	0.92	17 <sup>3)</sup>	18 <sup>3)</sup>	-1
108. 689 14-3-39	♀ Cancer of cervix uteri	R. St. No. 19641	78	4.02	0.96	19 <sup>3)</sup>	16 <sup>3)</sup>	3
109. 851 20-3-39	♀ Cancer of the breast	R. St. No. 20061	95	4.45	1.06	12	8	4
110. 707 20-3-39	♀ Caneer of uterus	R. St. No. 18563	64	4.39	0.72	33 <sup>3)</sup>	30 <sup>3)</sup>	3
111. 782 20-3-39	♀ Obs.	F. H. <sup>1)</sup> Dep.E.IF No. 268F	84	4.06	1.03	3	3	0
112. 893 20-3-39	♀ Arthritis deformans	F. H. Dep. E I No. 5399	82	—	—	3	2 black	1

<sup>1)</sup> F. H. = Fiisen Hospital.

<sup>2)</sup> R. St. = Radium Station.

<sup>3)</sup> Diffuse interface.



## REFERENCES.

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## SUMMARY.

*Introduction.* The significance of a combination of theory and experiment for the treatment of biological problems is emphasized.

*Section I.* Blood sedimentation in general.

§ 1. Some features from the history of blood sedimentation with special regard to the aggregation phenomenon are discussed.

§ 2. The difference between rouleaux formation and other erythrocyte aggregations is elucidated by a discussion of various types of real agglutination, *Thomsen-Friedenreich's* phenomenon, clustering together of red blood corpuscles in media which are poor in electrolytes, *etc.*

§§ 3—8. On the basis of *Stokes'* formula, the influence of a number of physical magnitudes on blood sedimentation is discussed (*e. g.* shape, size, specific gravity, aggregation, concentration of the erythrocytes, and viscosity of plasma and of whole blood). § 6 deals moreover with the correction of the sinking reaction for variations in the erythrocyte concentration, and § 8 contains some remarks concerning the aggregation promoting effect of emulsoids.

§§ 9—13 deal with the influence of the blood (plasma) composition as regards proteins, electrolytes, lipoids, gases, and some other substances.

§ 14 gives a description of the effect of temperature, and

§ 15 that of shaking on blood sedimentation.

§ 16. In view of the significance of the erythrocyte surface for the aggregation process, a number of recent investigations concerning the structure of erythrocytes are mentioned.

§ 17. Since the disc shape of the erythrocytes is a condition for rouleaux formation as an orientated aggregation, the effect of various suspension media on the shape of erythrocytes is discussed.

§ 18. The literature on special erythrocyte aggregation theories mentioned in the survey represents a very heterogeneous

material of rather differing value; some of the theories are only of historical interest. On account of the rôle which cataphoretic measurements play in experimental investigations of coagulation phenomena, this part of the blood sedimentation literature is described in detail. According to the author's opinion — which is in contradistinction to the interpretation of *Höber's* school — especially the discovery of a parallelism between erythrocyte charge and sinking reaction is of essential significance.

§ 19. The performance of sedimentation tests and an interpretation of the shape of the sinking reaction curve are outlined in brief.

*Section II.* A survey of the colloid physical problems which are of importance for the understanding of the mechanism of the sinking reaction.

§ 20 gives a detailed discussion of *Stokes'* formula with regard to its application to blood sedimentation.

§ 21. The influence of the walls of the vessels on the movement of falling particles and particles which move between plano-parallel planes is discussed.

§ 22 contains an outline of the theory of the Brownian movement of spherical and ellipsoidal particles and, moreover, the formulas for their principal resistance coefficients to translation and rotation.

§ 23 describes different theories of the electric double layer of colloidal particles with special regard to *H. A. Abramson* and *L. Moyer's* calculation of the erythrocyte charge and to the present author's new aggregation theory.

§ 24 exhibits a survey of the most important principles of coagulation measurements.

§ 25 describes the elements of the real coagulation theory, especially the "critical potential theory" and *H. Müller's* hypothesis concerning the variation of the thickness of the electric double layer, and a number of other theories.

§ 26. A classification is given of different types of coagulation (rapid and slow, peri- and orthokinetic coagulation, etc.) according to *G. Wiegner*.

§ 27. The basis of *M. v. Smoluchowski's* mathematical coagulation theory and the most essential literature dealing with its experimental application are described.

§ 28. *H. Müller's* theory of the perikinetie coagulation of poly-dispersive systems is discussed.

§ 29. *P. Tuorila's* work on orthokinetic coagulation is outlined in brief.

§ 30 comprehends *M. v. Smoluchowski's* and *H. Müller's* theories of streaming-coagulation.

§ 31. *H. Müller's* theory of the coagulation of non-spherical particles, and *G. Wiegner* and *C. E. Marshall's* experiments are described.

§ 32. A systematic discussion of the coagulation measurements which have been applied to blood corpuscle suspensions. Reference is also made to various phenomena which might be employed for this purpose. (*G. Wiegner's* suspension effect, *H. Fricke's* and others' observations concerning changes in conductivity of the blood).

*Section III.* The author's theoretical investigations.

§ 33. The application of *Smoluchowski's* coagulation theory to the problem of intercorpuscular attraction is elucidated by a mathematico-physical interpretation of the concept "action radius". By the solution of a more general diffusion problem than *Smoluchowski's* (*viz.* Brownian movements under the effect of an external force, *i. e.* diffusion with convection), and by a new solution of *Smoluchowski's* simultaneous differential equations for the number of particles, his formulas are reproduced and they only contain a new constant action radius. Hence, it has been possible to express the action radius by intercorpuscular forces which — in suitable cases — should be determinable by means of the method described in the following paragraph. If coagulation forces and action radius are determined on one and the same suspension, the calculated and the experimentally found action radius may be compared.

§ 34 describes the theory of the author's method of direct determination of coagulation forces. By kinematographic photographs of the movements of a pair of particles and by a measurement of the centre-line, the force function may be determined on the basis of the fundamental laws of mechanics. The influence of Brownian movements is eliminated by the study of numerous pairs of particles. The method can only be applied to systems



with far-range intercorpuseular forces. The results of §§ 33 and 34 have been published recently (*J. E. Thygesen*, 1939 (415)).

§ 35 contains an elementary derivation of the formula for the mean square of the displacement of ellipsoidal particles. By means of the formulas derived in § 22 for the resistance coefficients of ellipsoids, numerical examples for a given ellipsoid and, moreover, the equivalent radius of the ellipsoid are calculated.

§ 36. After a systematic discussion of the theory of the electric conductivity of suspensions, the possibilities for the appearance of a time-dependent change in conductivity are considered. Two possibilities are found to be of importance for the explanation of later experimental investigations. 1) Inclusion of the suspension medium within the conglomerates ("plasma occlusion"). 2) A change in the cataphoretic conductivity of the suspension due to aggregation. Finally, an approximate calculation of the cataphoretic conductivity of the blood is outlined.

§ 37 deals with the theoretico-physical investigation of the so-called "orientation effect". The results of this investigation have been published recently (*J. E. Thygesen*, 1939 (414)). For a suspension of homogeneous ellipsoids, where the particles and the suspension medium show different specific conductivities, a change in electric conductivity with time has been assumed. This change should be caused by an orientation of ellipsoids due to a rotation momentum, *viz.* the ponderomotive action of the electric field on ellipsoids. The effect is calculated for ellipsoids of revolution, only. By an orientation of the ellipsoids with their major axes parallel to the electric lines of flow, the conductivity effect is greatest and becomes least in the case of random orientation. For the calculation of the electric momentum of rotation acting upon an ellipsoid of revolution, *Fürth's* formula may be applied which holds with the assumption of quasistationary states. For the counteracting friction, we use *Edwardes'* formula. By means of a method which is analogous to that employed by *Debye* for polar molecules, a partition function is calculated which describes the orientation of the ellipsoids under the influence of an arbitrary electric field and of the Brownian molecular movements. Finally, and in agreement with *H. Fricke*, a formula for the conductivity of the suspension is derived assuming a given direction distribution of the ellipsoids of revolution which allows us to determine the con-

ductivity at a given time and to follow its change with time. In the case of completely haphazard direction distribution of the ellipsoids, the conductivity formula is identical with that derived by *H. Fricke*.

In a constant field, the conductivity is time-dependent and approximates a new constant value after a certain period (time of relaxation). This new constant value deviates somewhat from the value which corresponds to an equal distribution of directions. In the case of alternating potentials whose periods are low compared with the time of relaxation, the change in conductivity (orientation effect) is found to depend in a simple way on the change in conductivity during constant potential.

In suspensions where the conductivity of the ellipsoids is many times greater than that of the suspension medium, considerable effects may be obtained. If the conductivity of the suspension medium is many times greater than that of the particles (*e. g.* in blood), we find almost no effect. For very small particles, the effect becomes always negligibly small.

§ 38. On account of the technical difficulties involved by the direct measurement of forces (theory, § 34; experiments, § 41), which the author did not succeed in surmounting, a new theory of the attraction between blood corpuscles is outlined in a form which makes exact mathematico-physical calculations possible. It is the author's intention to publish these very complicated investigations in a work to come.

In a mechanical system consisting of particles between which attractive forces are active, we find a *van der Waals'* cohesion pressure. Independent of whether the attractive forces are electric forces or are of another nature, the equilibrium state can be calculated by means of *W. Thomson's* electrostatic minimum principle. In the case of erythrocytes, the forces are assumed to be electrostatic Coulomb forces which, due to the tendency of *Debye-Milner's* ionic atmosphere to attain central symmetry, compel the equally charged blood corpuscles to aggregate.

The author's aggregation theory is in agreement with the parallelism between erythrocyte charge and aggregation tendency and it offers a complete explanation of the resulting type of conglomeration (*rouleaux* formation) and of the influence of electrolytes and viscous substances upon the aggregation process.

Section IV. The author's experimental investigations.

A. Aggregation experiments.

§ 39 describes the preparation of the blood sample for the experiment, the photographic arrangement, the performance of the experiments, and the sources of error in the technique employed.

§ 40. On the basis of counting-aggregation experiments *ad modum Smoluchowski*, the characteristic distribution of the sizes of aggregates is elucidated. The coagulation is not monodispersive as originally assumed by *E. Ponder*. It is proved that rouleaux formation is a very intense polydispersive coagulation in which two- and threefold particles already act as nuclei of coagulation. The aggregation promoting effect of the polydispersivity is demonstrated by measurements on blood with varying sedimentation test.

As regards the temperature dependence of aggregation, it has been proved that the aggregation tendency decreases slowly with increasing temperature. The general view that this process increases with increasing temperature must presumably be ascribed to observations in slightly heated preparations (currents!).

In studies of the effect of emulsoids on rouleaux formation, tylose (methyl cellulose) has been employed, a substance which has not been applied earlier to this purpose. The degree of aggregation increases with increasing concentration of tylose and, moreover, the sinking reaction is also increased.

The influence of shaking on aggregation is found to be in agreement with *Smoluchowski's* interpretation. On the basis of these aggregation experiments, the possibility for orthokinetic coagulation during blood sedimentation is discussed. A number of phenomena exclude this type of coagulation which is not especially investigated in the present paper.

§ 41 describes filming of rouleaux formation. These experiments are an excellent supplement to the direct microscopical observation of red cell suspensions frequently applied during the present work. On account of erythrocyte sedimentation it has not been possible (until the conclusion of the present thesis) to surmount the technical difficulties involved in the direct measurement of coagulation forces.

### B. *Conductivity measurements.*

§ 42 contains a description of the author's special conductometric device and the application of the apparatus.

§ 43. The change in conductivity of blood after stirring, streaming, *etc.* found by *H. Fricke* and others is for the first time utilized rationally as a measure of coagulation.

The independence of the conductivity effect of sedimentation and the close relation to rouleaux formation are shown. An "orientation effect" cannot be demonstrated in the case of blood (*cf.* § 37). The relation between conductivity effect and blood sedimentation, erythrocyte concentration, and temperature is investigated. The conductivity effect is an expression for polydisperse coagulation. The experiments on the influence of stirring may elucidate streaming-coagulation which plays a great part in blood corpuscle suspensions. Small variations in the carbon dioxide content of the blood are without any influence on the conductivity effect.

When the conductivity phenomenon is interpreted as a change in cataphoretic conductivity of the blood, it becomes possible to give theoretically agreeing explanations for all conductivity experiments performed. Consequently, the author assumes that the electric charge of erythrocytes must be greater than communicated by *H. A. Abramson* and *L. Moyer*.

### C. *Metabolism hypothesis.*

§ 44. *N. Rashevsky* is of the opinion that the metabolism products of the cells can give rise to mutual effects of forces (between the cells) due to a formation of inhomogeneous fields of concentration in the suspension medium. Initiated by this hypothesis, the author investigates these circumstances in the case of red blood cells with a negative result. A number of metabolic poisons are added to the blood and the sedimentation rate is compared with that of control oxalate blood.

The *Appendix* contains tables and curves which illustrate the present investigations.

## MAIN RESULTS.

*Experimental.*

I. The proof that "rouleaux formation" is an intense poly-dispersive coagulation in which already two- and threefold particles act as nuclei of coagulation.

II. Development of a method of measuring coagulation by means of conductivity determinations. This method is based upon the change in cataphoretic conductivity during rouleaux formation.

*Theoretical.*

III. An extension of *Smoluchowski's* mathematical coagulation theory which now includes arbitrary intercorpuscular forces.

IV. A method of direct measurement of coagulation forces.

V. A mathematico-physical treatment of the so-called "orientation effect", *i. e.* the change in electric conductivity of a suspension of non-spherical particles which orientate in an electric field.

VI. An outline of a new theory concerning rouleaux formation of red blood corpuscles and an account for attractive forces between the equally charged blood corpuscles.

# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CXXXV

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## BOVINE TUBERCULOSIS IN MAN

A CLINICAL STUDY OF BOVINE TUBERCULOSIS,  
ESPECIALLY PULMONARY TUBERCULOSIS, IN  
THE SOUTHERNMOST PART OF SWEDEN

BY

*ERIK HEDVALL*

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## THE RELATION BETWEEN BOVINE AND HUMAN TUBERCULOSIS FROM THE VETERINARY POINT OF VIEW

BY

*HILDING MAGNUSSON*

# ACTA MEDICA SCANDINAVICA

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HELSINGFORS 1941



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persons for several months, the animals did not develop tuberculosis. GAISER (28) failed to produce tuberculosis in calves by means of pure cultures of tubercle bacilli from man, and the same result was obtained somewhat later by FROTHINGHAM (27) and DINWIDDIE (23). This problem was studied with especial care by THEOBALD SMITH (112—113), who reported extensive investigations in 1898. He pointed out differences between the bacilli isolated from man and from cattle. They differ not only in their morphological and cultural characters, but also in their pathogenic properties toward various animal species. Human tubercle bacilli are incapable of finding a foothold in the bovine body, but bovine tubercle bacilli may pass to the human subject, owing to their greater pathogenicity for man. According to SMITH's opinion, it was therefore necessary to differentiate between two different forms of *bacillus tuberculosis mammalinum*, viz. tubercle bacilli of the human and of the bovine type.

These investigations apparently did not arouse very much attention. The old view that tuberculosis in man and in cattle was caused by one and the same virus was still held rather generally. On the other hand, all the more interest was excited when R. KOCH (58) gave a report of his experiments in collaboration with SCHÜTZ at the International Congress on Tuberculosis held in London in 1901, which confirmed THEOBALD SMITH's conclusions. Tuberculin negative cattle had been infected in different ways with tubercle bacilli cultivated from man. Some of the cases got the tubercular sputum of consumptive patients direct. In some cases the tubercle bacilli or the sputum was injected under the skin, in others into the peritoneal cavity, and in others into the jugular vein. Six animals were fed with tubercular sputum almost daily for seven or eight months; four were repeatedly made to inhale large numbers of tubercle bacilli, which were distributed in water and scattered with it in the form of spray. None of the experimental animals showed any signs of disease, nor did the post-mortem examination 6—8 months later reveal any evidence of tuberculosis in the internal organs. Small suppurative foci containing tubercle bacilli were found only at the site of inoculation. But as similar foci were also observed after the injection of dead tubercle bacilli, the animals had thus proved themselves to be insusceptible. Quite

different results, however, were obtained when similar experiments were made with tubercle bacilli cultivated from cattle. No matter in what way the infection took place, the animals shortly afterwards developed extensive tuberculosis. Some of the animals succumbed already after 1—2 months, the others were slaughtered in a wretched condition after an interval of 3 months. At autopsy extensive tuberculous changes were found in all cases not only at the site of inoculation and in the adjacent lymph nodes but also in the internal organs, especially the lungs and the spleen. Thus the experimental animals had proved themselves to be as susceptible to bovine infection as they had been insusceptible to human. As exactly the same results were obtained in further experiments on swine, asses, sheep and goats, KOCH justly considered that he was in a position to make the following pronouncement: »I feel justified in maintaining that human tuberculosis differs from bovine, and cannot be transmitted to cattle». The next statement made by KOCH, which, among other things, was based on the rare occurrence of primary intestinal tuberculosis in the autopsy material of children from Berlin, created, however, a great deal of controversy: »I should estimate the extent of infection by the milk and flesh of tubercular cattle, and the butter made of their milk, as hardly greater than that of hereditary transmission, and I therefore do not deem it advisable to take any measures against it». In the following discussion, LISTER, NOCARD, BANG, SIMS WOODHEAD, MC FADYEAN and CROOKSHANK declared that they were not convinced that bovine tuberculosis was not dangerous to man, and seriously warned against relaxing the campaign against tuberculosis in cattle. KOCH's point of view met with contradiction also in Germany, especially by BEHRING (9).

This discussion resulted in investigators all over the whole devoting their energy and interest to the solution of this problem. In England the British Royal Commission on Tuberculosis was appointed, which presented a report of its results in 1911. In Germany the question was studied at the Kaiserliche Gesundheitsamt and in America at the Department of Health in New York. Their observations were published in 1908 and 1911 respectively. All these investigations, extending over many years, furnished conclusive proof that tuberculosis in warm-blooded animals can be

produced by 3 different types of tubercle bacilli, distinguishable from each other in their cultural and infectious properties, viz. the human, the bovine and the avian.

As far as man is concerned, these three types of bacilli play a very different rôle. The avian bacilli are by far the least important, and it is very doubtful whether they are pathogenic for man. Cases of avian tuberculosis in man have, however, been described. They are nevertheless extremely rare and not always quite convincing, as appears from the critical reviews by GASUL (30), BRANCH (13), TULLOCH (124) and GERVOIS (31). On the other hand, there is no doubt whatever as to the infectiousness of the bovine tubercle bacilli, which are capable of producing all the different manifestations of tuberculosis in man originating from human infection. They are, however, of decidedly less importance than the human tubercle bacillus, which is the commonest cause of human tuberculosis.

Bovine tuberculosis nevertheless occurs in man much more frequently than is generally supposed. Thus, with regard to conditions in Great Britain SAVAGE (108) wrote in 1934 «that about 6 per cent of all deaths from tuberculosis are caused by the bovine type of the tubercle bacillus; that about 2,000 deaths, mostly in children, occur annually from infections with the bovine tubercle bacillus; that at least 4,000 fresh cases of bovine infection occur each year. The majority do not die, but the infection results in severe crippling and other serious illnesses, causing much suffering and invalidity to the individuals and great expense to the community in an effort to cure them». Remarkably high figures are also recorded by L. LANGE (62), who states that bovine tubercle bacilli were found in 13.5 per cent of 1,165 typed cases of tuberculosis in man in Germany (up to 1936), in 26 per cent of 1,226 cases in Scotland (1932), in 10 per cent of 436 cases in Canada (1932) and in 4 per cent of 100 cases in Japan (1932). VAN DER HOEDEN (48) demonstrated bovine bacilli in 34 out of 423 tuberculous patients admitted to the University Clinic at Rotterdam (in sputa and gastric lavage 3.28 per cent, in urine 10.6 per cent, in cerebrospinal fluids 26.7 per cent, in pus 9.3 per cent, and also in 3 out of 15 bits of skin and in 1 out of 7 lymphatic glands). Of the patients examined 8.03 per cent had contracted a bovine infection (the corresponding figure for the whole of Holland was 7.13 per cent). In

1940 JENSEN, LESTER and TOLDERLUND (53) published the results of typings of tubercle bacilli made in Denmark during the years 1931—1936. Altogether 5,746 strains of tubercle bacilli from just as many cases of tuberculosis were typed. Of these no less than 644 (11.2 per cent) were bovine. The cases of bovine tuberculosis most frequently occurred in Jutland — and in particular, North, West and South Jutland — whereas the islands, especially the island of Bornholm, are practically free from bovine infection in man. In Sweden, the first cases of bovine tuberculosis in man were described by PETERSSON and KLING (89) in 1914. In an examination of 60 young children from Stockholm they found not less than 8 cases of bovine infection. In recent years small epidemics of bovine tuberculosis have been observed in different parts of Sweden and have been described by TÖRNELL (126—127), STÅHL (121), KAIJSER (55), OLSSON (79), GNOSSPELIUS (32), GARDELL (29) and FOGSTRAND (26). In a comprehensive work published in 1937 GERVOIS (31) has classified all cases recorded in the literature

Table 1<sup>1</sup>.  
*The Incidence of Bovine Tuberculosis in Man.*

Country	Total number	Human	Bovine	Bovine %
France (4, 7, 19, 22, 63, 100, 101, 106, 127)	1083	1055	28	2.6
Germany (62) .....	1165	1007	158	13.5
Netherlands (12, 64, 102, 103, 129) .....	767	701	66	8.6
Switzerland (96, 110, 118) .....	218	201	17	7.8
Norway (3, 10, 49, 119) .....	107	101	6	5.6
Poland (90) .....	160	149	11	6.9
Italy (6, 16, 20, 21, 36, 85, 109) .....	871	846	25	2.9
Spain (18) .....	95	90	5	5.3
Hungary (51, 122) .....	334	328	6	1.8
Greece (2) .....	327	327	0	0
Australia (84, 131, 132) .....	280	246	34	12.1
Japan (1, 56, 59, 69, 107, 133) .....	272	264	8	2.9
United States (5, 17, 24, 25, 34, 35, 47, 65, 66, 70, 78, 80—83, 97, 98, 114—116) ....	1362	1202	160	11.7
Canada (91—94) .....	901	847	54	6.0

<sup>1</sup> The investigations were carried out at quite different times. Some of the figures can hardly be regarded any longer as representative, for example those from the U.S.A. and Norway.



in which the bacilli were typed. According to this writer bovine tubercle bacilli had been found in 1912 out of 17,045 cases, which amounts to a percentage of nearly 11.2, exactly the same figure as for the Danish material. The majority of the bovine tuberculous changes were extrapulmonary, in the first place glandular and cutaneous tuberculosis, in the second place bone tuberculosis, tuberculosis of the meninges and urogenital tuberculosis. On the other hand, pulmonary tuberculosis was relatively rare. Finally, in 1939 PRICE (95) summarised the reported incidence in various countries (see Table 1).

All these investigations show very clearly the significant rôle played by bovine tuberculosis. But no generalisation should be attempted from these figures, for the incidence of tuberculosis in cattle differs widely in different countries, even in different parts of the same country. Nevertheless they indicate that the greatest possible attention should be devoted to this problem in future and that the campaign against tuberculosis in cattle should be continued by every available means.

### **B. Bovine pulmonary tuberculosis in man.**

When ROBERT KOCH at the International Tuberculosis Congress at Washington in 1908 still maintained his opinion that bovine infection was of little importance to man, he was able, among other things, to point to the fact that not a single case of bovine phthisis had been discovered. Such a case, it is true, had been described already in 1905 by DE JONGH (54) and STUURMAN (120), but as the bacilli behaved, at least to a certain extent, like the human type the case must be regarded as doubtful. The first two cases of indisputable bovine phthisis were observed in England by GRIFFITH (37, 38) in 1909.

One of these cases was a butcher's assistant, aged 21 years. He had had pneumonia and pleurisy ten months before admission to hospital and had suffered from cough ever since. When admitted there was consolidation of the upper part of the left lower lobe. Four specimens of his sputum were investigated. All contained numerous short tubercle bacilli. Cultures from the first sample, isolated through the guinea-pig, exhibited the cultural characters and the high virulence for the calf, rabbit and guinea-pig of a typical bovine tubercle bacillus. The other three samples were

collected at intervals of 76, 117 and 118 days respectively after the first. Cultures were obtained from each sample through the guinea-pig, and from the last two direct by means of antiformin. All the strains were identical in cultural characters with those first isolated and proved highly virulent for rabbits, the direct culture from the third specimen producing rapidly fatal tuberculosis in two calves inoculated subcutaneously. The other case reported by GRIFFITH was a bricklayer, aged 31 years. He suffered from pneumonia when 20 years old and from pleurisy four months before admission. When admitted there were signs of consolidation of both upper lobes. Two specimens of sputum were investigated; the second specimen was collected 118 days after the first. Both samples contained a moderate number of tubercle bacilli. The cultures isolated from the two specimens through the guinea-pig and from one specimen directly were very dysgonic and exhibited for calves, rabbits and guinea-pigs the high virulence of typical bovine tubercle bacilli.

From the protocols of the cases it is evident that there cannot be any doubt as to the correctness of GRIFFITH's interpretation of the observed cases. Thus bovine bacilli are capable of producing pulmonary tuberculosis in man. The establishment of this fact naturally led to further investigation, but during the next few years only isolated cases of bovine phthisis were observed. One case of this disease was described from Scotland by GRIFFITH (38) in 1913 and another from the same country by WANG (130) in 1916. One case was observed by PERGOLA (85) in Italy in 1918, while TULLOCH, MUNRO, ROSS and CUMMING (125) recorded 3 cases in 1924 and MUNRO (72, 74) 2 cases in 1928.

With the exception of PERGOLA's case, all the new cases were found in Scotland, the majority at the Fife and Kinross (Glenlomond) sanatorium, where systematic investigations have been carried on in this field since 1921. At first the purpose of these investigations was to determine whether there was any bacteriological differences in the strains, cultivated from sputum originating from 100 tuberculous persons. No such difference could be shown, it is true, but the various strains exhibited certain divergencies, the explanation of which was obtained when it was proved that two of them were bovine, one was mixed, i. e. contained both human and bovine tubercle bacilli, and the others were human. In the following years cultures were obtained from different tuberculous material. In two patients from whom they had obtained bovine bacilli from lesions of the sternum and of a rib respectively,

there were also pulmonary infiltrations. In both cases bovine tubercle bacilli were cultured also from the sputum. In 1928 the investigations were extended so as to include all patients admitted with pulmonary tuberculosis showing a positive sputum and any other tuberculous lesion. In that way it was possible, according to MUNRO and GRIFFITH (39, 44, 72—74, 125), to demonstrate 16 cases of bovine pulmonary tuberculosis in man in Scotland during the years 1924—1930. If we include the cases observed previously by GRIFFITH (38) and WANG (130), altogether 18 cases of this disease had been found in Scotland up to 1930, which amounts to about 3.8 per cent of the investigated material (468 cases).

The observations made in Scotland naturally stimulated further investigation in England and elsewhere, the results of which have shown that phthisis due to bovine tubercle bacilli is by no means a rare occurrence. Up to 1937 the total number of observed cases of this disease in England was not less than 194. According to GRIFFITH (43), the percentage of bovine pulmonary tuberculosis increases from less than 1 per cent in the south of England to 9 per cent in the rural districts of North-east Scotland. Six of the 52 bovine cases from North-east Scotland were found among 19 patients from the Orkney Isles, giving these islands the percentage of 31.5.

With regard to the number of observed cases of bovine pulmonary tuberculosis in man, Denmark comes next to Scotland and England. The problem of bovine tuberculosis has also been studied in that country very carefully, especially by K. A. JENSEN and his co-workers. As already mentioned, JENSEN, LESTER and TOLDERLUND (53) have shown that not less than 11.2 per cent of the investigated cases of tuberculosis were of bovine origin (644 out of 5,746 cases). Not a few of these cases were affected with bovine phthisis. Already in 1932 BEGTRUP HANSEN and K. A. JENSEN (8) described 2 cases of pulmonary tuberculosis due to the bovine tubercle bacillus. Since then TOBIESEN, JENSEN and LASSEN (123) have investigated 26 cases of bovine pulmonary tuberculosis in children and adults, practically all living in Copenhagen, and HAMMER (45) has recorded 20 cases of the same disease in adult age (16—37 years) from South Jutland. MOURIER (71) has observed and described another 33 cases from Jutland.

In Sweden the first cases of bovine phthisis were observed in 1936 by HEDVALL, LINDAU and MAGNUSSON. These cases, along with those discovered later, are described in detail in the present work. Two cases of the same disease were diagnosed by TÖRNELL (127) in the Province of Västergötland in 1938. Pulmonary tuberculosis developed from previous tuberculous changes in the tonsils and cervical lymph nodes after a latent period of 9—12 months.

In Finland and Norway, where the incidence of tuberculosis in cattle is much lower than in Sweden and Denmark, no case of this disease has been found so far. Quite recently BRANDT (14) published a report of extensive typings of bacilli made by him in Norway. Although no less than 1,065 specimens of sputum, 117 of gastric lavage and 42 of pleural exudate from phthisical persons were investigated not a single case of bovine origin was found among them.

In Germany bovine pulmonary tuberculosis has been subjected to an exhaustive study by BR. LANGE (60, 61), who has made valuable contributions especially to our knowledge of the epidemiology. The first 4 cases of bovine phthisis were described by him in 1931. Since then further cases have been recorded by BR. LANGE, by GOETERS (33) and by HÄMEL (50). The number of cases observed, however, is rather small.

Bovine phthisis has also been met with in other countries. Thus PRICE (95) states that in France 2 cases were found among 561 investigated (0.4 per cent) by SAENZ (105), D'ARCIER and D'ARCIER-BORREL (4). In Italy, PERGOIA (85), DADDI (20), DADDI and DI NATALE (21), SAVAGNONE (109) found 16 cases among 639 examined (2.4 per cent). In Hungary, SZÜLE (122) reports 2 cases among 206 phthisical persons investigated (0.9 per cent). In Poland, PIASECKA-ZEYLAND (90) diagnosed 3 cases out of 112 examined (2.7 per cent); and in Switzerland, MÜNDEL and STREMPER (76) found that out of 60 cases of pulmonary tuberculosis, 1 was due to the bovine bacillus (1.7 per cent). According to RUYs (104), the incidence of bovine pulmonary tuberculosis among the urban population of the Netherlands is 1 per cent, and that of the rural population 6 per cent.

In 1937 GERVOIS (31) gave the total number of published cases of bovine pulmonary tuberculosis in man at 260. As the number

of phthisical patients in which the bacilli had been typed amounted up to then to 8,536, this equals a percentage of 3; a remarkably high figure.

Thus bovine pulmonary tuberculosis in man is not so uncommon as is generally supposed. Now that workers are becoming more and more alive to this disease, there is every reason to assume that the number of observed cases will rapidly increase. It is obviously necessary that in places where tuberculosis in cattle is common every new case of pulmonary tuberculosis detected should be methodically investigated as to its human or bovine origin. In that way one will soon get to know whether the campaign against tuberculosis is being conducted along the correct lines and whether the protection against infection is sufficiently effective. What information may be gathered from such a methodical investigation will be seen from the following account.

## 2. The origin and planning of the investigation.

As already mentioned, investigations carried out in Denmark revealed a remarkably large number of cases of bovine tuberculosis in man. The southernmost part of Sweden (the Province of Skåne) lies on about the same degree of latitude as Denmark. Tuberculosis in cattle is common in this part of Sweden, and it was therefore quite natural that the question soon arose whether the incidence of bovine tuberculosis was as high among the population of Skåne as among that of Denmark. The necessity of a methodical investigation of the conditions became evident when LINDAU, in preliminary experiments, succeeded in finding solitary cases of this disease.

At a meeting of doctors and veterinarians from different parts of Skåne held at Malmö in December 1936 HEDVALL (46) submitted a plan, according to which the investigation should be conducted. The main purpose was to find out how often pulmonary tuberculosis in this part of Sweden was caused by bovine tubercle bacilli, and what significance was to be ascribed to this form of disease. At the same time the sources of infection and also the pathways of infection were to be studied in order to determine the measures that should be adopted to combat them. On the other hand, less importance was to be attached to ascertaining the number of cases of other forms of bovine tuberculosis, but specimens from such diseases sent in would of course also be investigated and studied. Thus no pressure was exercised to induce doctors to send in specimens from such patients, but on the other hand, thanks to an intimate cooperation with sanatorium doctors, hospital doctors and dispensaries, sputum was sent in for examination from the majority of the cases of infectious pulmonary tuberculosis.

In order to make the investigation as reliable and valuable as possible, the work was from the beginning carried out by a bacteriologist, a tuberculosis specialist and a veterinarian. The investigation of the specimens sent in and the typing of the bacilli were therefore performed by LINDAU. The observed cases of bovine tuberculosis as well as the patient's families were examined by HEDVALL, who was also responsible for the clinical analysis of the material, while the task of inspecting the herds and elucidating the possibilities of infection was entrusted to MAGNUSSON.

In the following pages an account will be given of my part of the investigation. The bacteriological and veterinary reports will be published in *Acta Medica Scandinavica*. Detailed information of the technique employed in typing the bacilli will be found in LINDAU's report, and has been briefly described by me in an earlier work in 1937 (46). All the strains of indubitable or suspected bovine appearance were tested on rabbits. There is therefore not the slightest doubt that the changes found in all the cases described were really of bovine origin. This is further supported by the fact that only bovine tubercle bacilli were found even when repeated typings were made in different material from the same patient. The investigation, which was carried on from 1936 to the summer of 1939, was performed with financial assistance from the Swedish National Society against Tuberculosis. The blocks were made at the Malmö Grafiska Anstalt. The radiograms were for the most part taken at the Roentgen-diagnostic Department of Lund Hospital (Chief: H. HELLMER, M. D.). The work has been translated by Mr. OWEN MORTON. To all those institutions, to sanatorium and hospital doctors, dispensary doctors and nurses who, by furnishing information about the patients and their families, by remitting the patients for examination, etc., have facilitated the carrying out of the work, I beg to express my sincere gratitude.

### 3. Clinical study of the observed cases of bovine tuberculosis in man.

As will be seen from the following chapters, bovine tuberculosis in man was found to be rather common in the southernmost part of Sweden (the Province of Skåne). The disease was also of a very serious character. In many cases the infection led to a fatal issue or resulted in a long period of disablement. From this it is evident that bovine tuberculosis can no longer be regarded mainly as a veterinary problem. Doctors, too, must participate more actively than formerly in the fight against this form of tuberculosis and not devote their attention almost exclusively to the prevention of the occurrence of *human* infection. Anti-tuberculosis work in future should therefore be characterised by an intimate cooperation between doctors and veterinarians.

In order to be able to carry on such an intensified campaign against tuberculosis with the greatest possible efficacy, it is necessary, however, to subject bovine tuberculosis, especially pulmonary tuberculosis, in man to a detailed study. It is not enough to find out in what part of Sweden this disease is most widely spread, so as to intensify the fight against *bovine* infection just in that locality; every doctor must also possess an intimate knowledge of the routes of infection and the different forms of disease following a bovine infection. The investigations in this field made especially in recent years have for the most part been devoted to bacterial and epidemiological conditions. The clinical features have also been dealt with, but in general relatively briefly, and only a few radiograms, illustrating the different manifestations of bovine tuberculosis in man, have been published.

In the following classification chief importance has been attached to the clinical features observed in the study of 67 cases of bovine



tuberculosis in man found in the Province of Skåne. Only those cases in which bovine tubercle bacilli were found have been included in the present series. The case histories have been made as detailed and concise as possible. In addition to the morbid changes present and the course of the disease itself, the source of infection is given in those cases where it was discovered. A great many radiograms have been included so that the reader can himself form an opinion of the appearance and the nature of the tuberculous changes at the time they were diagnosed.

The procedure in examining the patients and their environments was briefly as follows: As a rule the patient was admitted to and nursed at Lund Hospital for some time. Later he was, if necessary, transferred to a sanatorium or other institution. In some instances the patient had already been admitted to a sanatorium when the result of the typing of the tubercle bacilli became known. The examination was carried out in accordance with a definite plan. Attention was directed especially to the presence of rests of the primary infection in order to be able to ascertain the route of infection. Thus careful attention was given to the presence of tuberculosis of the cervical lymph nodes, calcifications in the hilar regions and in the lungs, calcified abdominal lymph nodes, etc. The tuberculous changes demonstrated were followed for a great many years and the development of the changes was recorded by means of a large series of radiograms. Tuberculin tests, guinea-pig inoculation with sputum and gastric lavage were the standard methods of examination. The small divergencies made from this system of examination are of no practical importance and were due, as a rule, to the fact that the patients were not treated at the same institution during the entire period of their illness. A point of greater importance is that a necropsy examination could not always be made of the fatal cases. Thus a *post-mortem* examination was made in only 12 of the 26 fatal cases. The cause of this was that either the patient died at home or necropsy examination was not permitted by the relatives.

During the time the patients were under observation or treatment their relatives were subjected to a careful examination, as a rule performed by me at the Central Dispensary in Lund. An X-ray examination of the lungs was always made. When the ex-

mination was completed and careful information had been obtained with regard to the occurrence of tuberculosis among the farm livestock, consumption of «raw» milk, etc., a record of the observations made was sent to the Royal Medical Board, who in appropriate cases appointed a veterinarian, generally H. MAGNUSSON, to perform a veterinary inspection of the cattle on the farm. The result of the investigation is given in the case histories.

### A. Case histories and radiograms.

*Case 1.* Female, aged 1. Father, farm-labourer, Stehag.

The mother has a stationary, non-bacillary, apical tuberculosis. Other members of the family healthy. No source of infection was discovered among the cattle on the farm.

The patient was examined on account of the mother's illness. No evidence of disease was detected, apart from *loss of appetite*. The tuberculin reaction was positive. The sedimentation rate was 10 mm. *No demonstrable tuberculous changes. Bovine tubercle bacilli* were found in the gastric lavage. The present state of health is good.

*Case 2.* Female, aged 5. Father, crofter, Löberöd.

A maternal aunt and an uncle died from pulmonary tuberculosis in 1929 and 1937 respectively, but the family had not met them for several years. The father had exudative pleurisy when 8 years old, but was now in good health. The mother and the youngest child (tuberculin negative up to 1 mg of tuberculin) were also well.

All the children living at home, with the exception of the youngest, became ill in June—July 1938, examination revealing, in addition to tuberculous changes, bovine tubercle bacilli in 3 of them (Cases 2—4). The other 3 children (not included in this classification) were also in all probability infected with bovine tuberculosis, although no tubercle bacilli could be demonstrated. On account of general symptoms of disease, such as *cough, lassitude, emaciation* and *fever*, they were given hospital care for several months. *One of them also developed erythema nodosum and a right-sided hilar adenitis.* The tuberculin reaction was positive (negative in the autumn of 1937).

The source of infection was most probably cows belonging to the farm. According to MAGNUSSON's report, there were before the children became ill no less than 3 cows in the small herd affected with open tuberculosis. One of these cows showed, when slaughtered, also tuberculosis of the kidneys, udder and uterus. *All the children with the exception of the youngest had drunk raw milk from these cows. The children used to play in the cow-house.*



Fig. 1.

Case 2. A 5-year-old girl (father, crofter) with *erythema nodosum* and a *tuberculous primary complex*. The hilar regions are enlarged and condensed. In the upper part of the left lung there is a compact density, partly due to tuberculosis, partly to atelectasis. *Bovine tubercle bacilli* were found in the sputum and in the gastric lavage. The changes reduced very slowly. The present condition is good. The patient belongs to a family in which 5 more children were infected by bovine bacilli at the same time. In addition to tuberculous changes, bovine tubercle bacilli were shown in 3 of these children (Cases 2—4).

The patient became ill in July 1938 with cough, vomitings, loss of appetite, fever and *erythema nodosum*. The tuberculin reaction, which was negative in the autumn of 1937, was now positive. The sedimentation rate was 37 mm, increased later to 53 mm, but returned to normal after 1 ½ months' hospital care. Radiograms of the lungs taken on 7th July 1938 revealed the presence of a bilateral hilar adenitis, also evidence of enlarged lymph nodes in the mediastinum, but no signs (calcifications, etc.) of a previous tuberculous infection could be detected. Three weeks later a compact

density could be observed in the left apical field, probably partly due to atelectasis, partly to tuberculosis (Fig. 1). The changes regressed very slowly. Thus as late as September 1940 the tuberculous changes in the left lung still remained. Radiography of the abdomen revealed no glandular calcifications. The lymph nodes of the neck were normal. *Bovine tubercle bacilli* were present in the sputum and in the gastric lavage.

A 5-year-old girl affected with *erythema nodosum* and *hilar adenitis with left-sided atelectasis and pulmonary tuberculosis* (primary complex). In all probability 6 of the 7 children in this family became ill as the result of a fresh infection with bovine tubercle bacilli. Bovine T.B. in the sputum as well as the stomach washing. The patient's health is at present good. The source of infection was most probably tuberculous cows on the farm.

*Case 3.* Male, aged 7 (brother of Cases 2 and 4). Father, crofter, Löberöd.

For family history and source of infection see Case 2.

The patient became ill in the middle of June 1938 with *cough, fatigue, stomach-ache, loose stools, loss of appetite* and *fever*. The stomach trouble disappeared after a short time but the cough remained. At the end of June *erythema nodosum* appeared. The tuberculin reaction was positive, and the sedimentation rate 29 mm (became normal after a few weeks). The radiograms of the lung taken in July 1938 showed a right-sided hilar adenitis (Fig. 2) and a small right-sided pleural exudation (visible in lateral view) but no evidence (calcifications, etc.) of a previous tuberculous infection. The hilar nodes gradually increased in size; in December 1938 a left-sided hilar adenitis could be observed, also signs of enlarged nodes in the mediastinum. Regression took place gradually. Radiographic examination of the abdomen showed no evidence of any glandular calcifications. The lymph nodes of the neck were normal. *Bovine tubercle bacilli* were found in the gastric lavage.

A 7-year-old boy, brother of Case 2, with *erythema nodosum* and *hilar adenitis* due to a fresh bovine tuberculous infection. Bovine T.B. in the gastric lavage. The patient's health is at present good. In all probability the source of infection was tuberculous cows belonging to the farm.

*Case 4.* Female, aged 10 (sister of Cases 2 and 3). Father, crofter, Löberöd.

For family history and source of infection see Case 2.

The patient became ill in the middle of June 1938 with *cough, fatigue, pain in the stomach, loose stools, fever* and *erythema nodosum*. The gastric



Fig. 2.

*Case 3.* A boy aged 7 years (brother of the preceding patient) with *erythema nodosum* and *tuberculous hilar adenitis*. The right hilar shadow is enlarged and condensed. *Bovine tubercle bacilli* were found in the gastric lavage. The hilar glands rather soon increased in size. Six months later a left-sided hilar adenitis also appeared as well as signs of enlarged lymph nodes in the mediastinum. Then followed a slow regression. The present health is good.

trouble disappeared after a short time but the cough remained unchanged. The tuberculin reaction was positive, the sedimentation rate was 45 mm (increased to 71 mm, returning to normal after two months). The radiograms of the lungs in June 1938 revealed a left-sided hilar adenitis but no signs (calcifications, etc.) of an earlier tuberculous infection. In July 1939 the hilar glands increased in size while at the same time changes appear-

ed in the centre of the left lung, which underwent regression later. Radiographic examination of the abdomen showed no glandular calcifications. No cervical gland tuberculosis occurred. *Bovine tubercle bacilli* were demonstrated in both the sputum and the gastric lavage in July 1938, in the sputum also in August 1939.

A 10-year-old girl (sister of Cases 2 and 3) exposed to a fresh infection with bovine tubercle bacilli, resulting in *erythema nodosum* and a *left-sided hilar adenitis*. Bovine T.B. in both sputum and gastric lavage. The present health is good. The source of infection was in all probability tuberculous cows belonging to the farm.

*Case 5.* Male, aged 16. Father, farm-labourer, Vintrie.

The parents and 2 of the 6 children living at home are in good health. The other children fell ill at the same time in March 1937 with symptoms of a fresh tuberculous infection; tubercle bacilli (of the bovine type) could be shown in only one of them (Case 5). There is no doubt, however, that the other children (not included in this classification) were also infected with bovine tuberculosis. One of them, for instance, had *erythema nodosum*, another *erythema nodosum* and a *primary complex in the right lung*, while a third showed *symptoms of abdominal gland tuberculosis*. All of them were in need of hospital care.

The source of infection was in all probability a cow that had been ill for about a month; the animal was unable to stand on its legs. When slaughtered on 10th March 1937 the animal was found to be affected with disseminated tuberculosis. *All the children had drunk raw milk and had often been in the cow-house.*

The patient became ill in March 1937 with *fatigue, stomach-ache, fever* and *erythema nodosum*. The stools were normal. The radiograms of the lungs revealed a *left-sided hilar adenitis* and a small parenchymal change just below the left hilum, on the other hand no signs (calcifications, etc.) of an earlier tuberculous infection could be detected. The tuberculin reaction was positive, the sedimentation rate 9 mm. A radiographic examination of the abdomen showed no glandular calcifications. The cervical lymph nodes were normal. *Bovine tubercle bacilli* were found in the gastric lavage.

A 16-year-old boy, belonging to a family in which in all probability 4 of the 6 children fell ill as the result of a fresh bovine tuberculous infection. *Erythema nodosum, left-sided hilar adenitis* and *pulmonary tuberculosis* (primary complex) developed. The changes showed a slow regression. Bovine tubercle bacilli were present in the gastric lavage. The other children, in whom no

tubercle bacilli could be demonstrated, had either erythema nodosum alone or erythema nodosum and a primary complex in the right lung or evidence of tuberculosis of the abdominal glands. The source of infection was probably a tuberculous cow belonging to the farm. The patient's health is at present good.

*Case 6.* Male, aged 29. Farmer, Esperöd.

Family in good health. No source of infection was discovered among the live-stock of the farm. The patient had tended cattle, milked occasionally and also consumed raw milk.

At Christmas-time, 1938, the patient had *cough, scanty expectoration and a stitch in the chest, mostly pronounced behind the sternum*. On the other hand, no fatigue or gastric trouble. The tuberculin reaction was positive and the rate of sedimentation 113 mm (fell to 28 mm after a month). Radiographic examination of the lungs in February 1939 revealed an extensive right-sided hilar adenitis and parenchymal changes in the dorsal part of the right lower lobe (primary complex), but no evidence (calcifications, etc.) of a previous tuberculous infection could be observed (Fig. 3). The changes, which were of a mottled appearance, regressed slowly. The cervical lymph nodes were normal. *Bovine tubercle bacilli were found in the sputum and in the gastric lavage.*

A 29-year-old man with *right-sided hilar adenitis and pulmonary tuberculosis* (primary complex) due to a fresh primary bovine infection. Bovine T.B. in the sputum and the gastric lavage. The present health is good. The source of infection has not been traced.

*Case 7.* Male, aged 14. Father, farmer, Rynge.

There was no family history of tuberculosis. The other children gave a negative tuberculin reaction. No source of infection could be found among the live-stock of the farm.

In 1938 the patient had been employed as farm-labourer at an uncle's farm in Bjärsjö. The history of this family was free from tuberculosis. Tuberculous disease had, however, occurred previously among the cattle on the farm. After the patient's infection, one of the cows was slaughtered owing to open pulmonary tuberculosis. The patient had looked after and milked this cow; he had also drunk raw milk from the farm.

In October 1938 the patient felt *tired*, had a *stitch in the left side of the chest and cough*. Shortly afterwards he developed *fever*, which necessitated hospital care. On admission *the tuberculin reaction was negative, but became strongly positive rather soon*. The rate of sedimentation was 50 mm, and showed no tendency to return to normal. Radiographic examination of the lungs in October 1938 revealed a left-sided hilar adenitis and pulmo-



Fig. 3.

*Case 6.* A 29-year-old farmer with a *tuberculous primary complex*. The right hilar shadow is considerably enlarged and condensed. Parenchymal changes occurred below the hilar region (in the posterior part of the right lower lobe). *Bovine tubercle bacilli* were demonstrated in the sputum and in the gastric lavage. The changes have reduced very slowly. The patient is at present well.

nary changes, probably in a large measure due to atelectasis (Fig. 4). On the other hand, no evidence of a previous tuberculous infection (calcifications, etc.) could be discovered. In later radiograms (8th November 1939) a parenchymal change as large as a hazel-nut could be observed below the hilar region (Fig. 5). Radiogram of the abdomen did not show any glandular calcifications. The lymph nodes of the neck were normal. *Bovine tubercle bacilli* were demonstrated in the sputum and in the gastric lavage.

Later the patient developed symptoms of tuberculoma of the cerebellum, and he died in November 1939. *Bovine tubercle bacilli* were also shown in the tuberculoma.



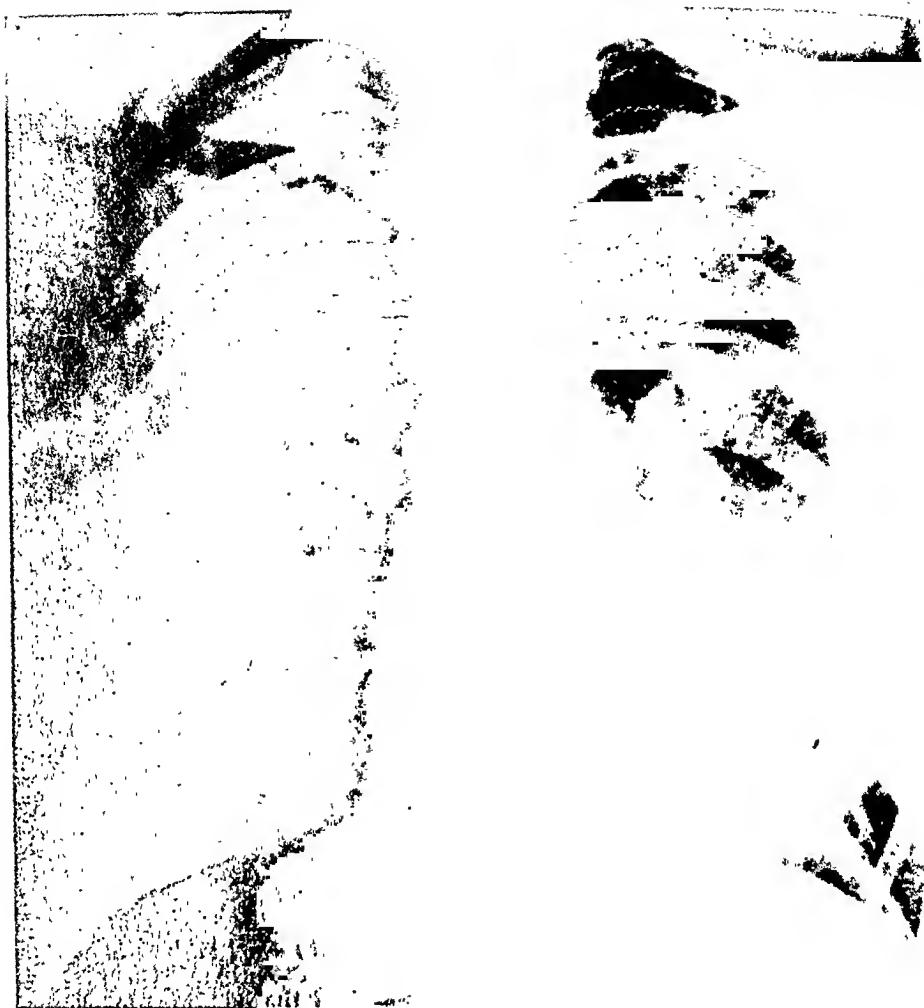


Fig. 4.

*Case 7. A boy aged 14 years (father, farmer) with a tuberculous primary complex. The left hilar shadow is enlarged. In the lower part of the left lung there is a compact density, partly due to tuberculosis, partly to atelectasis. Bovine tubercle bacilli were present in the sputum and in the gastric lavage.*

*Autopsy (performed by Prof. E. SJÖVALL):*

The right lung was normally air-cushioned and without any palpably solid areas, the pleura smooth and glossy. The juice that could be pressed out of the tissue was normally frothy and clear, and from the bronchi emerged a thick, yellowish white mucus. The left lung was of a normally air-cushioned consistency everywhere with the exception of the area immediately lateral of and above the hilum, where a resistance of a more solid

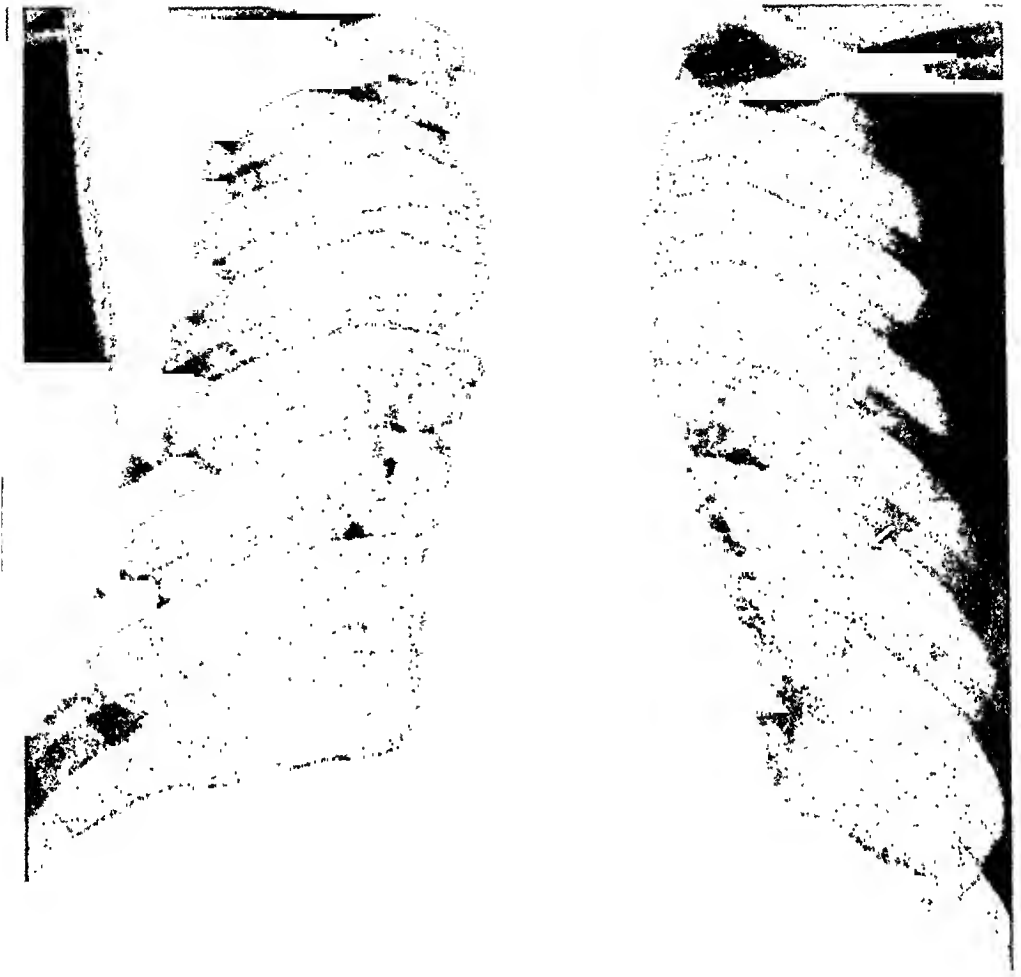


Fig. 5.

*Case 7.* (The same case as in Fig. 4). The changes reduced gradually. A year later a density could still be seen within an area as large as a hazel-nut below the left hilar region. The patient died from a *tuberculoma of the cerebellum* shortly afterwards. Bovine tubercle bacilli were also shown in the tuberculoma.

consistency about twice the size of a walnut could be palpated. Along the main bronchus of the left hilum, at the bifurcation and along the left side of the trachea, there were several nodes varying in size from a bean to a hazel-nut, rather solid and with small white, degenerating, caseous foci on the cut surface. On the right side of the trachea there were only a few pea-sized nodes, but these, too, were taken up by small caseous foci. No changed glands were met with in the right hilum. The pleura of the left lung was everywhere smooth and glossy. Both lobes of the lung were widely fused together by means of adhesions of connective tissue. On the

cut surface the lower lobe was quite normal apart from the thick exudate issuing from the bronchi. Corresponding to the area in which resistances were palpated, there was in the upper lobe a firm indurated area of connective tissue, dark red in colour, with ill-defined margins and without any caseous or necrotic areas. The tissue was not aerated, but no cloudy juice could be pressed out of it. No calcifications could be found anywhere, either in the glands or in the lung tissue. Abdominal cavity: The peritoneum was smooth and glossy; no increase of fluid; the topographical conditions normal. Appendix had been removed. Nodes, varying in size from a bean to a hazel-nut, which felt rather firm and on the cut surface often showed small caseous necroses, were palpable in the mesentery of the coecum and here and there in that of the small intestine. The intestinal mucosa was everywhere normal, no ulcers, no redness, no scar-formation after old sores were macroscopically discernible . . . . . On being removed the left hemisphere of the cerebellum, which was very loose in consistency, was broken and a very solid body, about twice the size of a walnut, was pushed out of a bed composed of a composite, degenerating, whitish grey cerebellar substance . . . . . On section the surface was found to be homogeneous, yellowish white, almost glossy (like a raw-peeled potato), with a narrow, light greyish red border at the periphery. No liquefaction, no haemorrhages. The right hemisphere of the cerebellum showed no abnormality.

The *neecropsy diagnosis* was: Tbc. pulmobronchial. sin. in sanatione. The solitaria cerebelli.

A 14-year-old boy with *left-sided hilar adenitis and pulmonary tuberculosis* (primary complex), due to a fresh primary bovine infection. About a year later he developed a *tuberculoma* of the cerebellum, and he died about 1 year after the onset of the tuberculous affection. Bovine T. B. were present in the sputum, the stomach washing and in the tuberculoma. The source of infection was in all probability a cow affected with open pulmonary tuberculosis belonging to the farm at which the patient had been employed.

*Case 8.* Female, aged 7. Father, farmer, Rynge.

Parents and 8 brothers and sisters in good health. *An elder, married sister has cavernous phthisis with abundant bovine tubercle bacilli in the sputum* (Case 49). The cattle belonging to the farm are healthy. The patient has not been absent from home for more than a day at most, except when she attended village school at Vallösa for two terms. No case of tuberculosis is said to have occurred in her class at school. The farm has a rather isolated location. At home the patient came into contact only with her parents and brothers and sisters; the milk she drank always originated from the farm's own production. The source of infection was the phthisical sister.



Fig. 6.

*Case 8.* A girl of 7 years (father, farmer) with *erythema nodosum* and a *tuberculous primary complex*. The left hilar shadow is enlarged and condensed. On rotation (Fig. 7) a small parenchymal opacity is seen also on the left side — the lung component of the primary complex. *Bovine tubercle bacilli* were found in the gastric lavage. The source of infection was an elder sister with bovine phthisis (Case 49, Fig. 19). See also text to Fig. 7.

The patient was subjectively well until July 1938, when she had an eruption of *erythema nodosum* with subsequent *subfebrility*. No abdominal symptoms. The tuberculin reaction was positive, the sedimentation rate 50 mm (fell to 11 mm one month later). Radiographic examination of the lungs on 3rd July 1938 revealed a left-sided hilar adenitis but no evidence (calcifications, etc.) of a previous tuberculous infection (Fig. 6). After a month or two a small parenchymal opacity appeared also below and behind



Fig. 7.

Case 5. (The same case as shown in Fig. 6). The picture, taken with the left shoulder rotated forwards, shows the small parenchymal density. The primary complex afterwards reduced gradually. The present health is good.

the left hilum (Fig. 7). The changes slowly regressed. The cervical lymph nodes were normal. Radiogram of the abdomen showed no glandular calcifications. *Bovine tubercle bacilli* were found in the gastric lavage.

A 7-year-old girl exposed to a fresh primary infection of the bovine type, resulting in *erythema nodosum* and a *left-sided hilar adenitis* and *pulmonary tuberculosis* (primary complex). Bovine T.B. in the gastric lavage. The patient's condition is at present good. The source of infection was an elder sister affected with bovine phthisis (Case 49).

Case 9. Male, aged 23. Veterinary student, Höör. Father, bank director. No family history of tuberculosis.

When studying at the Veterinary College, Stockholm, the patient, according to his own report, handled much tuberculous material at the laboratory and the slaughter-house. In May 1937, while working at Stockholm, he had *erythema nodosum*. No abdominal symptoms. The tuberculin reaction was positive and the rate of sedimentation increased. Radiographic examination of the lungs on 8th May 1937 revealed a right-sided hilar adenitis and parenchymal changes below and behind the right hilum (primary complex). The lymph nodes of the neck were normal. The changes regressed very slowly. *Bovine tubercle bacilli were present in the sputum.*

A 23-year-old man with *erythema nodosum and right-sided hilar adenitis and pulmonary tuberculosis* (primary complex) due to a fresh primary bovine infection. Bovine T. B. in the sputum. Present health good. The source of infection was probably bovine material with which the patient had come into contact during his veterinary studies.

*Case 10.* Female, aged 30. Unmarried, living at home. Father, crofter, St. Herrestad.

Parents and brothers and sisters in good health. The source of infection was a cow on the farm that had been ill and had had a cough for a long time. This animal was slaughtered in the autumn of 1935 and was then found to be «full of tuberculosis». The patient had milked this cow and also drunk raw milk from it.

The patient became ill in April 1935 with *cough, fatigue, loss of weight and stitch in the left side of the back*. On the other hand, she had no abdominal symptoms. The tuberculin reaction was positive and the rate of sedimentation 36 mm. A radiographic examination in May the same year revealed the presence of a left-sided hilar adenitis and lung changes centrally on the same side, together with a considerable widening of the mediastinum, indicating also the presence of enlarged nodes there (primary complex) (Figs. 8—9). On the other hand, no evidence of an earlier tuberculous infection (calcifications, etc.) was discernible. The cervical lymph nodes were normal. The lung changes soon showed all indications of a malignant development. The mediastinal lymph nodes increased considerably in size. On account of suspected liquefaction in the changed area in the left lung pneumothorax was induced, which had to be interrupted after a short time, however, owing to the development of a bilateral exudative pleurisy, which caused marked dyspnoea. The condition afterwards became more and more deteriorated and the patient died in June 1936. *Bovine tubercle bacilli were cultivated from the pleural fluid and from the lung tissue* (see necropsy report).

*Necropsy report* (performed by Prof. E. SJÖVALL) was as follows:

When the large body cavities were opened, a wide dissemination of

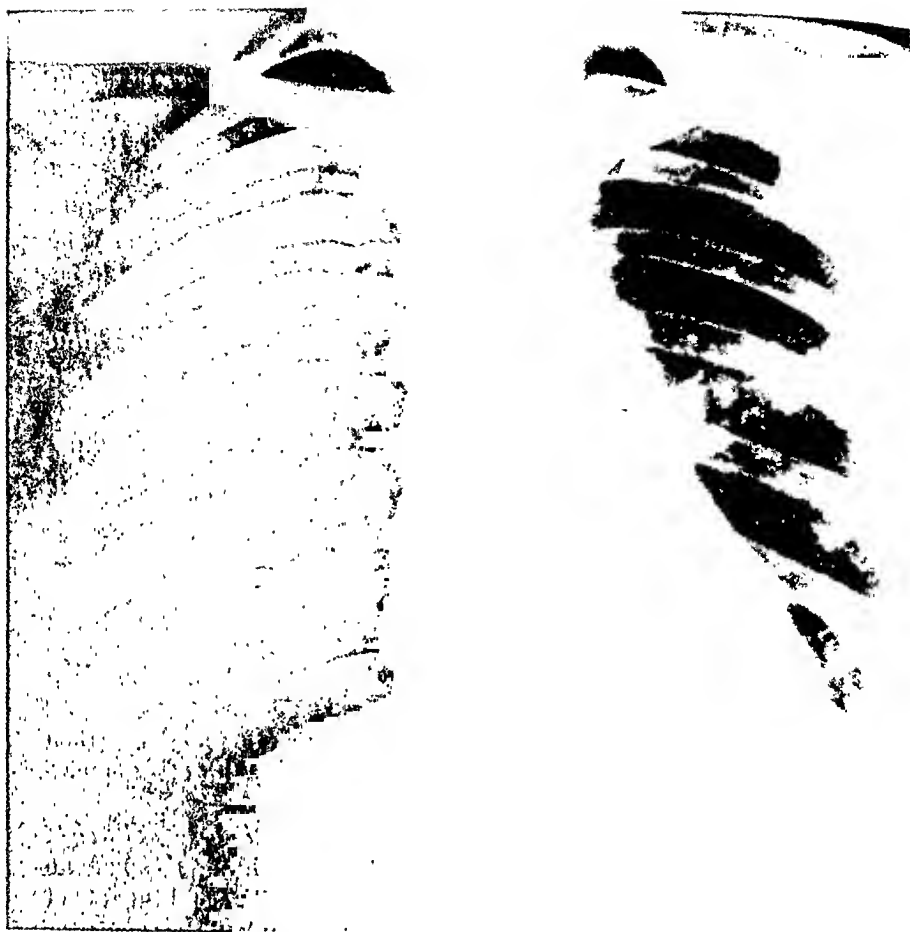


Fig. 8.

*Case 10.* An unmarried woman aged 30 (father, farmer) with a *tuberculous primary complex*. The left hilar shadow is enlarged and moderately condensed. Outside this area, towards the centre of the left lung field, there were also parenchymal changes covering an area about the size of a hazel-nut (the lung component of the primary complex). See also text to Fig. 9.

small and large, frequently plainly caseous tubercles was seen everywhere in the pleurae and in the peritoneum. Not infrequently these tubercles clustered together into large mats, and on the surface of the lungs there was an organised fibrinous membrane, dotted with nodules. Such a membrane entirely enclosed the greatly collapsed left lung like a sac, and it was not until this membrane was removed — with difficulty — that the contours of the lobes of the lung were plainly seen. In the abdominal cavity the tuberculous process united with extensive adhesions, particularly thick and continuous in the right subphrenic space. Evidence of acute serositis



Fig. 9.

*Case 10.* (The same case as in Fig. 8.) The lung component appears more clearly in this picture, taken with the left shoulder rotated slightly forwards. The disease ran a malignant course. Haematogenous dissemination took place to the serous membranes and several organs. Death occurred about 13 months after the diagnosis of the primary complex. *Bovine tubercle bacilli* were cultivated from the pleural fluid and from the lung tissue (on post-mortem examination).

was met with only in the form of a fresh fibrinous coating at the bottom of the anterior part of the right lung. The pericardium was unchanged. When the thoracic viscera had been removed, all lymph nodes on both sides of the trachea and round both main bronchi were found to be greatly enlarged, firm, entirely caseous but non-liquefying. The process continued with the same character and intensity right into the left hilum, and connecting on to this there was, at the base of the lateral part of the left upper lobe of the lung, a sharply defined focus of rather inspissated caseous tissue almost as large as a hazel-nut. Close around this focus there were some small, acinous, caseous foci. Otherwise no indications of tuberculosis other than a few diffusely spread, small tubercles were found in both lungs.



In the right upper lung lobe, however, there was a plum-sized pneumonic focus with central liquefaction and actively hyperaemic in the proximity of the surrounding. The heart was rather small, flaccid and pale, otherwise without any changes. The liver was intensely pale, not very rich in fat, and the spleen showed a fairly normal appearance. No miliary tubercles were observed in these organs. Tubercles were, however, found in the otherwise unchanged kidneys, small tubercles occurring in some places in the cortex. The internal genital organs showed gross serosal changes of tuberculous nature, but were otherwise normal. The lymph nodes round the truncus coeliacus were caseously degenerated. The mesenteric lymph nodes and the intestinal mucosa showed no evidence of tuberculosis.

The *necropsy diagnosis* was: Tbc. prim. caseosa pulm. sin. et lymphogland. bronchial. et tracheae + polyserosit. tbc. + tbc. mil. mitior pulm. et renum + pneumonia lob. sup. dxt. c. necros.

A 30-year-old woman with *left-sided hilar adenitis, pulmonary tuberculosis and tuberculosis of the mediastinal lymph nodes* (primary complex) due to a fresh primary bovine infection. Later *miliary dissemination* took place to the serous membranes and to a number of the organs of the body. The patient died about 13 months after the affection had been diagnosed. Bovine T.B. were demonstrated in the pleural exudate and the lung tissue. In all probability the source of infection was a tuberculous cow on the farm.

*Case 11.* Male, aged 6. Father, church-caretaker, Dalby.

Parents and other children healthy. An uncle had pulmonary tuberculosis in 1926 (thoracoplasty in 1928) but recovered and has been nonbacillary for quite a long time. Formerly the father used to slaughter animals but, according to report, has not done so for many years. The family does not keep any cows, milk having been brought from different sources. The patient has drunk raw milk. The source of infection has not been discovered.

In the beginning of April 1936 the patient had mumps. In the middle of April he felt *fatigued*, had *vomiting*, *loss of appetite*, and some days later he developed *headaches*, *photophobia* and *fever*. He showed the usual signs of tuberculous meningitis. An X-ray examination of the lungs showed the picture of miliary tuberculosis but no evidence (calcifications, etc.) of a previous tuberculous infection (Fig. 10). He died on 22nd May 1936. *Bovine tubercle bacilli were present in the cerebrospinal fluid.*

*Necropsy* (performed by Dr. A. Sjövall) gave the following result:

The dura mater was tense, hyperaemic. The soft membranes were hyperaemic but dry; the gyri were flattened. At the base of the brain there was a plastic, greenish grey, gelatinous exudate, and along the vessels



Fig. 10.

*Case 11. A boy of 6 years (father, church-caretake) with bovine primary tuberculosis of the abdomen and acute miliary tuberculosis as well as tuberculous meningitis, resulting in death after a short time. The diffuse, minute granularity typical of miliary tuberculosis is shown in the picture. Bovine tubercle bacilli were found in the cerebrospinal fluid.*

up towards the convexity there were scattered tubercles varying in size from a pin-head to a grain. The tonsils and cervical lymph nodes were normal. No primary complex within the region of the lungs. High up in the jejunum there was a small ulcer, barely the size of a grain, in the mucous membrane; the corresponding mesenteric lymph nodes were caseously

yellowish white. The heart and the pericardium were quite normal. The pleura was also normal. Diffuse, typical miliary tubercles, the size of hemp-seeds and yellowish white in colour, in the lungs, which showed no changes otherwise. In the liver and in the somewhat enlarged spleen there were also numerous miliary tubercles. Apart from what was said above, the digestive canal showed no abnormalities. Likewise the peritoneum, the pancreas and the bile ducts. In both renal pelvises and in one place in the bladder there were quite fresh ulcerations of tuberculous appearance about the size of pin-heads. Otherwise the urinary organs were normal.

The *necropsy diagnosis* was: Tbc. primaria intestini tenuis et lymphogland. mesenterii + Tbc. miliaris + Meningitis tbc.

A 6-year-old boy with *bovine primary tuberculosis in the abdomen and acute miliary tuberculosis and tuberculous meningitis*, leading to death. Bovine T.B. were present in the cerebrospinal fluid. The source of infection was not traced.

*Case 12.* Male, aged 15 months. Father, groom. Vadensjö.

Parents and other children healthy. The source of infection was established. The investigation proved that at the age of 8—13 months, i. e. for a period of 5 months, the child had been given milk from a herd in which 3 cases of open pulmonary tuberculosis occurred among the cows.

In December 1937 the patient had a *fracture of the skull* due to a fall. After an interval of good health the patient again fell ill on 31st May 1938 with *attacks of cramp and periods of apathy*. He showed the usual symptoms of meningitis. Died on 8th June 1938. *Bovine tubercle bacilli present in the cerebrospinal fluid.*

The *necropsy examination* (performed by Dr. LINDSTEN) detected: Lungs everywhere aeriferous, soft, homogeneous in consistency. A few scattered, pin-head-sized, yellowish white nodules on the pleural surface. On section the lung tissue was found to be somewhat dry, but otherwise showed no abnormality. The heart and pericardium normal. The peritoneum was everywhere smooth and glossy. On the surface of the liver there were several miliary, yellowish white nodules, solitary nodules being also found on the cut surface. The spleen was small, rather solid and interspersed with numerous yellowish white foci up to the size of pin-heads. The kidneys normal. The mesenterial lymph nodes were swollen to the size of walnuts, partly medullary, partly transformed into a caseous mass. The meninges were abnormally tense. The cisterns and sulci contained a greyish gelatinous exudate. Numerous, small adhesions between the dura and the arachnoidea, but which could be easily separated on removal of the brain. Numerous, miliary, greyish white nodules along the vessels and in the choroid plexes. The ventricles were somewhat distended. Otherwise there were no abnormalities.

The *necropsy diagnosis* was: Tbc. lymphogland. mesenterii + tbc. miliaris hepatis, lienis et pulmonum + meningit. tbc.

A 15-month-old child with *bovine primary tuberculosis in the abdomen* and *acute miliary tuberculosis* and *tuberculous meningitis*. Died. Bovine T.B. in the cerebrospinal fluid. Source of infection was discovered.

*Case 13.* Female, aged 7 months. Father, farmer, Ramsåsa.

An aunt died of pulmonary tuberculosis many years ago. Parents and other children healthy. The patient had consumed raw milk from the farm. No veterinary examination of the herd was made. The source of infection has not been traced.

When 1 month old the patient had vomitings for a week or two. In July 1936, at the age of 7 months, she had attacks of *vomitings* again. Began to *lose weight* and had *fever*. *Evacuation of the bowels* 0—2 times daily, stools at first normal, later *somewhat mucous and watery*. Diagnosis: tuberculous meningitis. The tuberculin reaction was positive, and the rate of sedimentation 15 mm. *Bovine tubercle bacilli were found in the cerebrospinal fluid*. When the diagnosis had been made, the parents took the child home, where it died after a week. There was no necropsy.

A 7-month-old child died from *bovine tuberculous meningitis*. Bovine T.B. in the cerebrospinal fluid. The source of infection was not discovered.

*Case 14.* Female, aged 23. Unmarried daughter living at home. Father, farmer, Glemmingebro.

Father died of cancer in 1935. In the same year a sister died from «pneumonia». Other members of the family in good health. An examination of the cattle on the farm disclosed 3 cases of contagious pulmonary tuberculosis (one of the cows having a less pronounced, the other two advanced pulmonary tuberculosis). Attention had previously been called to the presence of tuberculosis in slaughtered animals from the herd. *The patient had tended and milked the cows, but «had not drunk any milk for 15 years»*, as she was not fond of milk. In all probability the source of infection in this case was the tuberculous cattle belonging to the farm.

The patient, who had not previously shown any symptoms of tuberculosis, became ill in November 1935 with *fatigue, stitch in the left side of the chest* and *fever*. In December she developed *dyspnoea* and a *cough*. The rate of sedimentation was 83 mm (falling to normal 1 month later). Radiographic examination of the lungs revealed no evidence (calcifications, etc.) of a previous tuberculous infection, but on the other hand showed a large exudate shadow on the left side, which necessitated repeated thora-

cocentesis. A radiogram of the abdomen taken in November 1937 and another in November 1938 did not show any glandular calcifications. The cervical lymph nodes were normal. *Bovine tubercle bacilli* were demonstrated in the pleural exudate.

A 23-year-old woman with *bovine exudative pleurisy*. Bovine T.B. in the pleural exudate. The source of infection was most probably tuberculous cows on the farm. The patient's present health is good.

*Case 15.* Male, aged 41. Parish constable, Vollsjö.

No history of tuberculosis in the family. Before becoming ill the patient had owned a cow suspected of tuberculous infection. No veterinary examination, however, was made. The source of infection has not been traced.

In April 1934 the patient had *pain in the lumbar region, swelling of the ankle-joint and left knee-joint and pain in the right elbow, the right forearm and the right metacarpophalangeal joint*. Some days later he had *erythema nodosum*. The tuberculin reaction was positive; rate of sedimentation 54 mm. No tuberculosis of the cervical lymph nodes occurred. Radiographic examination of the lungs showed increased density of the hilar shadows on the right side and outside this a mottled lung shadow. A collection of mottled parenchymal shadows could also be observed in the left infraclavicular fossa. Guinea-pig inoculation with gastric lavage gave a negative result. The diagnosis was: *erythema nodosum + pulmonary tuberculosis (primary complex and incipient lung changes) + acute polyarthritis*. The joint symptoms gradually disappeared and have not since recurred. In January 1936 the patient again had *shivering-fits, dry cough* but no stitches. A left-sided exudative pleurisy was diagnosed. The apical changes on the right side were still of the same appearance as formerly. *Bovine tubercle bacilli* were present in the pleural exudate. The condition gradually improved. The patient's present health is excellent.

A 41-year-old man with a fresh tuberculous infection, resulting in *erythema nodosum, a right-sided primary complex and left-sided incipient pulmonary tuberculosis*. About 17 months later he developed *bovine exudative pleurisy*. Bovine T.B. in the pleural exudate. The patient's present health is good. The source of infection was not discovered.

*Case 16.* Male, aged 16 months. Father, farm-labourer, Bara.

Parents and other children healthy. Two of the children, aged 3 and 4 respectively, were however tuberculin positive, but no tuberculous changes could be demonstrated. When about 12 months old the patient began to

drink raw milk from a herd, in which a few months later 1 cow was condemned owing to tuberculosis of the udder and lungs and 2 cows had been previously slaughtered because of pulmonary tuberculosis. Thus the source of infection was probably the tuberculous cows belonging to the farm in question.

After a long period of petulence and excessive perspiration the patient became ill in June 1938 with *cough, fever, loss of appetite and loose stools*; he had also *«a pain in the chest»*. The patient was tuberculin positive, and the sedimentation rate was 25 mm. The cervical lymph nodes were normal. The radiograms of the lungs was also normal, without any signs of an earlier tuberculous infection (calcifications, etc.). The X-ray examination of the abdomen showed the presence of meteorism and ascites. Death occurred a few weeks later from tuberculous peritonitis. *Bovine tubercle bacilli were found (at autopsy) in the mesenterial lymph nodes.*

The *necropsy examination* (performed by Prof. A. LINDAU) gave the following result: Pericardium and pleural sac showed nothing abnormal. No enlarged nodes in the lung-hilum region. By pressing the lungs a yellowish, cloudy fluid was forced out of the bronchi. No evidence of tuberculosis anywhere in the lungs. No infiltration, but a diffuse bronchitis. When the abdominal cavity was opened, a moderate quantity of a clear, serous fluid ran out. The intestines were tympanitically distended. The wall of the stomach had ruptured owing to autodigestion, and a yellowish green, thick mush oozed out. The abdominal organs were fused together into a single packet and had to be removed in a body. Here and there between the intestinal coils there were caseous masses. The mesenterial lymph nodes were swollen and the cut surface was white and fatty. The retroperitoneal nodes were normal. The spleen was normal in appearance and consistency. No tubercles could be observed macroscopically. The liver was normal in size, pale but of normal outline.

The *necropsy diagnosis* was: Peritonitis tuberculosa + Rachitis.

A 16-month-old child with *bovine primary infection of the abdomen and tuberculous peritonitis*. Died. Bovine T.B. were found in the mesenterial lymph nodes. The source of infection was probably tuberculous cows on the farm.

*Case 17.* Male, aged 10 months. Father, groom, Genarp.

Parents and other children healthy. A half-brother, who had also consumed raw milk from the farm mentioned below, was admitted to hospital in 1939 under the diagnosis of lymphom. tbc. coll. + tbc. lymphogland. bronchial. Bovine tubercle bacilli were found in the gastric lavage. (This case has not been included in the classification, as it occurred after the investigation had been terminated).

The patient, born on 9th June 1938, had been fed on mother's milk for about 6 months, but from December 1938 to about 3 weeks before the onset

of the disease he had received raw milk from a herd, in which no less than 13 cows were found to be affected with open pulmonary tuberculosis in a clinical examination made in November 1939. The source of infection in both the above cases may thus be said to be established.

In April 1939 the patient had *fever* and *loose stools* (generally 3 evacuations daily, the stools being fetid and mucous). On the other hand, he had no vomitings. The tuberculin reaction was positive, and the sedimentation rate 36 mm. The cervical lymph nodes were normal. The radiograms of the lungs were normal, without any evidence (calcifications, etc.) of a previous tuberculous infection. The radiogram of the abdomen revealed the presence of fluid in the abdomen. The diagnosis was tuberculous peritonitis. Death occurred some weeks later owing to a perforation of a tuberculous intestinal ulcer. *Bovine tubercle bacille* were found at autopsy in the mesenterial lymph nodes and in pus from the abdomen.

The *necropsy examination* (performed by Dr. S. WINBLAD) gave the following result: The lung parenchyma was everywhere aeriferous. No evidence of pneumonia or tuberculosis anywhere. The peritoneum contained about 1 litre of a green, purulent fluid, indicative of a non-specific kind of peritonitis. Under the large layers of fibrin, which coated the serosa, there was, especially on the transverse mesocolon, a nodular tuberculous peritonitis. The surface of the liver was coated with peritonitic fibrin. No changes were observed on the cut surface. The spleen was normal in size and without any macroscopic changes on the cut surface. The pancreas and the bile ducts were normal. No changes could be seen in the stomach. In the intestinal mucosa, chiefly in the lower portion of the ileum, there were numerous, typical, tuberculous ulcers, sometimes in the form of rings. In the colon these ulcerations were extremely sparse. One of the ulcers in the lower ileum was perforated in the centre. No other spontaneous perforations could be observed, but in separating the numerous fibrinous membranes, the intestine ruptured in several places, where it was obviously thin. The kidneys were normal in size and showed no changes on the cut surface. On the left side there was a constriction of the ureter, just at the location of the large packets of nodes in the ileocaecal region. There was also a slight distension above that point.

The *necropsy diagnosis* was: Primary intestinal tuberculosis with multiple intestinal ulcers, tuberculosis of the mesenterial lymph nodes with caseous liquefactions, tuberculosis of the peritoneum + peritonitis from perforating intestinal ulcers.

A 10-month-old child with *fresh primary intestinal tuberculosis* and *tuberculosis of the peritoneum*. Death took place owing to a perforation from an intestinal ulcer. Bovine T.B. were found in the mesenterial lymph nodes and in pus from the abdomen. The source of infection was probably tuberculous cows on the farm.

*Case 18.* Female, aged 15 months. Father, unskilled labourer, Dalby.

Father healthy. In a radiogram of the abdomen the mother showed a conglomerate of hazel-nut-sized glandular calcifications as large as a goose's egg situated in the median line on a level with  $L_1$  and  $L_2$ , also calcifications the size of grains of rice in the upper part of the abdomen, which may represent calcifications in the liver, the spleen or the peritoneum (bovine tuberculosis?). A sister, who was admitted to hospital in 1938 on account of a transient cloudy density, the size of the palm of a man's hand, in the right middle lobe (bronchiopneumonia?) also showed a mass of bean-sized calcifications in the abdomen (calcified mesenteric nodes, bovine tuberculosis?). Another sister had a conglomerate of calcifications, together as large as a broad-bean, above the middle part of the sacrum (bovine tuberculosis?). Three other sisters had an increased rate of sedimentation for a long time, without any other morbid symptoms or demonstrable changes (abdominal lymph node tuberculosis?).

The family obtained milk from a neighbouring farm, where a cow was found to be affected with open pulmonary tuberculosis in June 1937. In October of the same year another cow was diagnosed with tuberculosis of the udder. Thus the source of infection may be regarded as established.

In November 1937 the patient had a bean-sized nodule on the crown of the head, which soon increased in size and ruptured. The sore gradually became larger. A microscopic examination of the tissue showed no tuberculous changes. Lymph nodes varying in size from a hazel-nut to a plum, however, were found on the neck right up to the nape. *The patient was now tuberculin positive, after being negative in August of the same year.* The rate of sedimentation was 32 mm. The radiograms of the lungs and the abdomen were normal. *The gastric lavage contained bovine tubercle bacilli.*

A 15-month-old child belonging to a family showing signs of a previous tuberculosis of the abdominal lymph nodes (bovine?). The patient developed *tuberculosis of the cervical lymph nodes* due to a fresh bovine tuberculous infection. Bovine T.B. were present in the gastric lavage. The source of infection may have been tuberculous cows on a farm from which the family had obtained milk. The patient's present health is good.

*Case 19.* Male, aged 3. Father, farmer, Klasaröd.

Parents and other children in good health. The patient had drunk raw milk from the farm. No veterinary examination was made. The source of infection was not discovered.

The patient had not previously shown any symptoms of tuberculous disease. In April 1937 he had parotitis. Shortly afterwards the mother noticed on the child's neck a resistance, not quite as large as a hazel-nut,



which rapidly increased in size to that of a pigeon's egg. The tuberculin reaction was positive. The liquefied lymphoma was scraped. *The granulations* showed the usual appearance of tuberculosis and contained *bovine tubercle bacilli*. The radiograms of the lungs were normal, without any evidence (calcifications, etc.) of an earlier tuberculous infection. The roentgenographic examination of the abdomen revealed no calcified lymph nodes. The patient died from tuberculosis of the lymph nodes in February 1938.

*Necropsy* (performed by Dr. S. WINBLAD on 26th February 1938): On the left side of the neck there were large packets of lymph nodes, partly caseous, partly, haemorrhagically enlarged. No fistula running towards the larynx could be observed. The mucous membrane of the larynx appeared to be greatly swollen and was also wrinkled (due to a glottic oedema?). The larynx as well as the trachea were intensely reddened and coated with a greasy secretion, extending far down into the bronchi. Both lungs were firmly adherent. No tuberculous or other kind of foci were visible on the cut surface. The heart was normal.

Minute white nodules (miliary tubercles?) were found on the surface of the liver and of the spleen, partly caseous lymph nodes, the size of almonds, in the angle between the coecum and the ileum. Large, swollen non-caseous lymph nodes along the radix mesenterii. In the intestinal lumen, in an area in the upper colon and the lower ileum, there were fresh, haemorrhagic ulcers in addition to an intense general swelling of the lymphatic areas. The kidneys showed no changes.

*Microscopic examination:* The intestinal ulcers were found to be of a tuberculous nature. Miliary tuberculous foci in the lungs, the liver and the spleen. The meninges were intensely infiltrated with lymphocytes, but no tuberculous foci were discernible. The larynx was intensely inflamed, submucously infiltrated. No specific changes were present here.

The *necropsy diagnosis* was: Caseous primary tuberculosis of the lymph nodes on the left side of the neck + caseous tuberculosis of the mesenterial lymph nodes at the coecal region + tuberculosis of the mesenterial lymph nodes + intestinal tuberculosis of a haemorrhagic type + miliary dissemination of tuberculosis in the lungs, the spleen and the liver + meningitis (tuberculous?) + laryngitis (probably of streptococcal origin).

A 3-year-old child with *primary tuberculosis of the cervical lymph nodes* and secondary tuberculosis of the lymph nodes in various places in the body and also miliary dissemination to several organs (lungs, spleen, liver, etc.). Died about 10 months after the disease had been diagnosed. Bovine T.B. in granulations from the lymph nodes. The source of infection was not discovered.

*Case 20.* Male, aged 5. Father, farm-labourer, Sjöbo.

Parents and other children healthy. The patient had consumed raw

milk from a farm, the owner of which is a slaughterer and cattle-dealer and consequently frequently exchanges animals. Nothing is known as to whether tuberculosis had occurred among the animals or not. No veterinary examination was made. The source of infection has not been detected.

The patient, who had not previously manifested any symptoms of tuberculous affection, had a sore throat in August 1937. In connexion with this affection there appeared on the neck a redness above a resistance, which the parents had not noticed previously. The tuberculin reaction was positive, and the sedimentation rate 10 mm. A conglomerate of enlarged lymph nodes, the size of a hen's egg, could now be seen just below the right mandible. The diagnosis was: tuberculosis of the cervical lymph nodes + tonsillar hypertrophy. In December the same year the nodes were scraped and extirpated, and in February 1938 tonsillectomy + abrasio were performed. On microscopic examination the *tonsillar tissue* showed well developed lymphatic tissue with numerous follicles, but no signs of tuberculosis. On cultivation, however, a few colonies appeared, which *were found to be bovine*. Radiograms of the lungs were normal, revealing no signs (calcifications, etc.) of a previous tuberculous infection. The patient's health is good and he has not manifested any symptoms from the nodes in the past year.

A 5-year-old child with *tuberculosis of the tonsils and cervical lymph nodes* (primary complex?). Bovine T.B. in the tonsillar tissue. The source of infection was not found. The patient's present health is good.

*Case 21.* Female, aged 21. Married. Husband, stone-cutter, Björns-torp.

Other members of the family healthy. During the years 1931—1935 the patient had been employed as milkmaid in different farms. It is not known whether tuberculosis occurred among the cattle on these farms. No clinical examination of the animals was performed. The patient got married in 1935, and since then has purchased milk from farms in the vicinity. No veterinary examination of the cows was made. The source of infection has not been traced.

In September 1937 the patient noticed a node as large as a walnut on the left side of the neck. During the first week this node was somewhat painful but afterwards the local symptoms disappeared. No abdominal symptoms. The tuberculin reaction was positive, the rate of sedimentation 15 mm. The diagnosis was: tuberculous cervical lymphomata. The *lymphomata* were excised and on microscopical examination were found to contain typical tuberculous changes. The *tubercle bacilli* were of the *bovine* type. The radiograms of the lungs were normal, revealing no evidence (calcifications, etc.) of a previous tuberculous infection.

A 21-year-old woman with *tuberculosis of the cervical lymph nodes*. Bovine T.B. were present in the lymphomata. The source of infection was not detected. The patient's health is at present good.

*Case 22.* Male, aged 17. Metal-worker, Arlöv. Father, farm-labourer, Ö. Sallerup.

Parents and brothers and sisters in good health. The patient has not milked or attended cows. The source of infection could not be traced.

In 1934, when only 14 years of age, the patient had been treated at a hospital for tuberculosis of the cervical lymph nodes. Incisions were made on both sides of the neck. In October 1936 he was again admitted owing to the appearance of new tuberculous lymph nodes on the neck. In February 1938 he was admitted for the third time for the same affection, this time to Lund Hospital. The cervical nodes had increased in size, and the patient now felt fatigued. No abdominal complaints. The tuberculin reaction was positive and the sedimentation 19 mm. The nodes were punctured, later extirpated. *Bovine tubercle bacilli were found in the punctate.*

A 17-year-old youth who had had *tuberculosis of the cervical lymph nodes* ever since he was 14 years of age. Bovine T.B. were found in the punctate from the tuberculous nodes. The patient's present health is good. The source of infection was not discovered.

*Case 23.* Male, aged 7. Father, taxi-driver, Lund.

The family history is free from tuberculosis. Five cousins of the mother, however, have died from tuberculosis. Four of them died before the patient was born, the fifth, who died in 1934, the patient met only once during a short visit. The family lived previously at the village of Löddeköpinge. Milk was purchased from travelling salesmen. The milk was not pasteurised or from non-reactive cows. The tuberculous changes appeared about 6 months after the family had moved to Lund, where the milk was bought at a milk-shop. The source of infection has not been traced.

Tuberculosis of the cervical lymph nodes was observed in 1935, for which the patient was treated several times at a seaside sanatorium. In October 1936 he developed quinsy and acute left-sided otitis and mastoiditis. Mastoidectomy was made. In December the same year a bilateral tonsillectomy was also performed. Tuberculous changes were found in the tonsillar specimen. *The tubercle bacilli were of the bovine type.* The patient is at present troubled with asthma.

A 7-year-old boy with *tuberculosis of the cervical lymph nodes and tuberculosis of the tonsils* (primary complex?). Bovine T.B. were

found in the tonsillar tissue. The source of infection has not been discovered. Apart from the asthma, the patient's present health is good.

*Case 24.* Female, aged 4. Father, transport-worker, Trelleborg.

The grandmother on the father's side died from pulmonary tuberculosis. An aunt has pulmonary tuberculosis of human origin but has been non-infectious since November 1937. Three children of this aunt have tuberculosis. One of them has tuberculosis of the bronchial lymph nodes, another tuberculosis of the left lung (non-bacillary), while the third had an exudative pleurisy in 1938 and has now also developed tuberculous osteitis. The father has a healed pulmonary tuberculosis. The mother and the other children are healthy. The family obtained milk from a dairy at Trelleborg. The patient has met his aunt and cousins only a few times. The source of infection has not been established.

At the age of 2 years the patient had *phlyctena* and at about the same time a *nodule on the neck*. This nodule gradually increased in size, especially in connexion with a cold in April 1938. The tuberculin reaction was at that time positive and the sedimentation rate 12 mm. Radiographic examination of the lungs revealed a right-sided hilar adenitis and a central parenchymal density on the same side, which subsequently disappeared, however, after a short time. Calcified spots could be shown roentgenologically in the enlarged cervical nodes but not within the regions of the lungs and hili. *Bovine tubercle bacilli were found in the gastric lavage*. While at the hospital the patient again developed phlyctenular keratoconjunctivitis. The patient is at present well.

A 4-year-old child, belonging to a tuberculous family, with *phlyctena, tuberculosis of the cervical lymph nodes and transient infiltration in the right lung with hilar adenitis*. Bovine T.B. in the gastric lavage. The source of infection was not traced. The patient's present health is good.

*Case 25.* Male, aged 5. Father, farmer, Onslunda.

The grandfather on the father's side has pulmonary tuberculosis (bacilli of the human type), but the patient has met him only a few times. An uncle had pulmonary tuberculosis during his military service 10 years ago, but is at present quite healthy. The parents and other children of the family are in good health. The father is a cattle-dealer and keeps the purchased animals in his possession for only a week or so. The family have consumed raw milk from cows belonging to the farm. It is not known whether bovine tuberculosis occurred or not.

In February 1936 the patient began to walk with *a limp in the right leg* and had *a pain in the right knee*. Ultimately he preferred to remain sitting

rather than walk about. The *pain increased*, becoming more and more intense. He was not admitted to hospital for treatment until October 1936, when the diagnosis of coxitis, tuberculous abscess, was made. The tuberculin reaction was positive, the rate of sedimentation 30 mm. *Bovine tubercle bacilli were found in the punctate from the abscess*. Radiography of the lungs was normal, the films showed no signs (calcifications, etc.) of a previous tuberculous infection. The patient is at present doing well and attends school regularly.

A 5-year-old child, belonging to a tuberculous family, with severe *tuberculosis of the hip-joint* and an abscess. Bovine T.B. present in the abscess. The source of infection is not known. The patient's present health is good.

*Case 26.* Male (blind and imbecile), aged 20. Father, tenant-farmer, Dalby.

An uncle has a healed tuberculous spondylitis. The parents and other children are healthy. Tuberculosis has, however, occurred in the animals on the farm. The patient lived at home until he was 11 years old, but had afterwards been at a Home for the Blind affected with Complicated Physical Defects. However, he used to spend the summer months at home and it is quite possible that he contracted bovine infection while living there. No veterinary investigation was performed. The source of infection was not traced.

The patient had a normal birth. On the third day of life he was seized with cramp. Blindness was noticed when he was 9 months old. He learned to walk and speak in normal time. He had epileptic fits occasionally. Signs of a gluteal abscess appeared in February 1936. The tuberculin reaction was then positive, and the rate of sedimentation 50 mm. No radiograms of the lungs were taken, but an X-ray film of the skeleton revealed a walnut-sized tuberculous focus in the posterior part of the os ileum. 500 cm<sup>3</sup> of a thick, brownish, odourless fluid, containing bovine tubercle bacilli, was drained from the abscess. The condition then rapidly deteriorated and the patient died in June the same year.

A 20-year-old man (blind and imbecile) with *bone tuberculosis* and an abscess. Died. Bovine T.B. were found in the punctate from the abscess. The source of infection was not discovered.

*Case 27.* Male, aged 6. Father, manufacturer, Båstad.

Parents healthy. A younger brother, aged 2 years, in good health. No tuberculosis in the family history. The source of infection could not be traced. Milk was obtained from a dairy.

In January 1936 the patient felt *tired*, had a *poor appetite*, *vomitings* and *fever*. He *lost* so much *weight* that he eventually became nothing but *skin and bones*. *Albumin appeared in the urine*. During a long confinement to bed his condition gradually improved and the albuminuria disappeared. After getting up the patient was observed to have a difficulty in walking. He had no pain, however, but in April 1936 he began to *drag the right leg*. The leg now *felt weaker*, sometimes it also *ached*. The diagnosis of tuberculosis of the right trochanter with abscess was made in September, which involved a long period of treatment. The tuberculin reaction was strongly positive, the sedimentation rate 59 mm. *Bovine tubercle bacilli were found in the punctate from the abscess*. The patient's present health is good and he is able to attend school. .

A 6-year-old boy with *bone tuberculosis* and an abscess. Bovine T.B. present in the punctate from the abscess. The source of infection is not known. The patient is at present in good health.

*Case 28.* Female, aged 62. Husband, farmer, Aggarp.

The parents died from decrepitude. A brother died from pneumonia (in association with measles). Other brothers and sisters healthy. The husband and the daughter (35 years of age) are in good health. The family kept a farm 2 years ago, usually having a herd of 4 cows, the milk from which was used at home. The patient milked the cows herself, and the animals are said to have been in good health. The farm was sold 2 years ago, but the patient is still living in the farm-house. The source of infection has not been traced.

In August 1932 the patient had *pain in the right elbow-joint*, which at Christmas-time the same year *became red and swollen*. In 1933 she was treated at a hospital for 3 months for *tbc. epicond. med. humeri dx.* An excision of a fistula and scraping the tuberculous focus were performed. She was again admitted to hospital in 1937 and was treated for 8 months for *tbc. cubiti dx. c. abscess*. *The punctate from the abscess contained bovine tubercle bacilli*. The X-ray examination of the lungs revealed a calcified primary complex within the region of the right lung and hilus. The radiograms of the abdomen showed nothing abnormal. The patient's condition is at present rather poor, but is due to decrepitude (permanently bedridden) and not to her earlier tuberculosis. In April 1940 the radiograms of the lungs were normal.

A 62-year-old woman, who 5 years previously had *tbc. epicond. med. humeri dx.*, now developed *tbc. cubiti dx. c. abscess*. A calcified primary complex could be observed in the area of the right lung and hilus. Bovine T.B. were present in the punctate from the abscess. The source of infection has not been traced. The patient's present health is very poor (decrepitude).

*Case 29.* Female, aged 29. Unmarried, living at home. Father, farmer, Löberöd.

Parents healthy. A twin-brother died in infancy (cause of illness?). A brother died from pulmonary tuberculosis in 1935 (the bacilli were not typed); a sister was primarily infected in the same year (the X-ray film of the lungs showed a typical picture of a tuberculous primary complex). The family used the milk from their own cows, which on veterinary examination were found to be in good health. The patient also took part in milking. The source of infection may have been the brother who died in 1935.

In January 1937 the patient had *pain and swelling in the right knee-joint*. The tuberculin reaction was positive, the rate of sedimentation 25 mm. The diagnosis was: *Gonit. tbc. Bovine tubercle bacilli were found in the punctate from the knee-joint*. Radiographic examination of the lungs in April 1937 revealed several rather large spots centrally on the left side. The lung changes regressed very slowly. Guinea-pig tests with sputum gave negative results. No cervical node tuberculosis occurred. Radiography of the abdomen made in September 1938 showed nothing abnormal.

A 29-year-old woman with *tuberculosis of the knee-joint and pulmonary tuberculosis*. Bovine T.B. could be shown only in the punctate from the knee-joint. The source of infection was perhaps a brother who died from pulmonary tuberculosis in 1935. The patient's health is at present good.

*Case 30.* Male, aged 29. Agent, Lund.

Parents and other children, the patient's wife and children in good health. Ever since youth the patient had temporary employment at different farms, where he also took part in milking. He has consumed raw milk. It is not known whether tuberculosis occurred among the cattle he came into contact with. In recent years the patient has been working as an agent in Lund. The milk has been obtained from a dairy in the town. It has not been possible to trace the source of infection.

In April 1935 the patient had epididymit. ac. sept. supp. An abscess cavity, containing staphylococcus pus, was drained. Guinea-pig tests with urine gave positive results. The patient was now recommended to go to hospital for treatment, but he refused to do so. He did not return for examination until February 1939, when he was found to have a resistance the size of a hen's egg in the right half of the scrotum, in the anterior part of which the testis could be defined. The orifice of a fistula could be seen on the outside of the scrotum. New guinea-pig inoculations with urine were made, which *showed the presence of bovine tubercle bacilli*. The rate of sedimentation was 7 mm. No definite evidence of renal tu-

berculosis was obtained however. The diagnosis was: *Fistula scroti post epididymit. tuberculosa*. The patient is at present doing well and is able to work. The symptoms from the urogenital organs are only slight.

A 29-year-old man with *tuberculosis in the right epididymis* (kidneys?). Bovine T.B. in the urine. The source of infection was not discovered. The patient's present health is good. He is fully capable of working.

*Case 31.* Female, aged 23. Domestic servant, Lund. Father, farmer.

The father died from pulmonary tuberculosis in 1912, the mother from heart disease in 1927. Up to 1935 the patient lived in the country (at Norrvidinge), where she drank raw milk from tuberculin-reactive cows. She also took part in milking. Nothing definite is known as to whether tuberculous changes occurred among the cattle. After 1935 she was employed, a short time before the onset of the disease, as a domestic servant in Lund. The source of infection has not been traced.

In February 1936 the patient became acutely ill with *frequent micturitions and pain in the left side of the abdomen, radiating out towards the back and down towards the urethra*; she was treated for a short time at a hospital under the suspicion of nephrolithiasis and renal tuberculosis. The rate of sedimentation was 5 mm. In May the same year she was re-admitted to hospital. The diagnosis was: *Bursitis tbc. tuberosit. tibiae et nephropathia sin. (tbc.? calculi?)*. Guinea-pig tests with urine were later positive, and *the bacilli were found to be of the bovine type*. The left kidney was removed in July 1936, minor tuberculous changes being found in the tissue. The lowest papilla of the kidney was ulcerated. In the corresponding pyramid there were some non-liquified tubercles. The radiographic examination of the lungs made at that time and in October 1940 showed nothing abnormal, no evidence (calcifications, etc.) of a previous tuberculous infection could be seen. The patient is doing well.

A 23-year-old woman with *bursitis tbc. tuberosit. tibiae et tbc. ren. sin.* Bovine T.B. in the urine. The patient's present health is good. The source of infection was not found.

*Case 32.* Female, aged 28. Wife of a brick-yard worker, Anderslöv.

No family history of tuberculosis. Before getting married the patient was employed as milkmaid at a farm and had consumed raw milk. It is not known whether tuberculosis occurred among the cattle. The source of infection was not found.



In September 1918 the patient noticed that the *urine was reddish* in colour. Some months later she complained of *painful and frequent micturations* and a *pain over the left hip-joint*. Left-sided renal tuberculosis was diagnosed. Nephrectomy was performed in February 1919. In the upper part of the kidney extensive cavernous lesions. The patient did well after the operation but had to urinate 3—4 times at night and every second or third hour in the day. In April 1936 she felt a tenderness below the right costal arch, which led to a re-examination. The *urine* again showed an aseptic pyuria. Guinea-pig inoculations with urine gave positive results. *Bovine tubercle bacilli* were found. The present health of the patient is good.

A 28-year-old woman with *bilateral renal tuberculosis*. Bovine T.B. in the urine. The source of infection was not discovered. The patient's present health is good.

*Case 33. Female, aged 28. Shop-assistant, Vollsjö.*

The father died in 1914, insane. The mother and other children of the family healthy. The patient, who was born at Gävle, lived for some years at Alvesta, afterwards in the country village of Vollsjö. Since the age of 14—15 she has been assisting her mother in the latter's shop. She has never had anything to do with cattle. The milk was obtained from a milk-shop. The source of infection has not been traced.

In October 1932 the patient had severe *attacks of pain* in the left side of the back, at about the lower margin of the chest. The pain felt like stabs and radiated up towards the left shoulder. The attacks recurred later at intervals of a few months. In May 1933 she began to complain of *frequent micturition*. On examination the patient was found to be tuberculin positive and to have a sedimentation rate of 58 mm. Aseptic pyuria was diagnosed, due to a left-sided renal tuberculosis. The radiogram of the lungs was normal. Nephrectomy was performed almost immediately. The parenchyma of the kidney was dotted with tubercles, particularly the central portion. In October 1934 guinea-pig inoculations with *urine* from the right kidney also gave positive results. Another test made in March 1936 gave the same result. *The tubercle bacilli were of the bovine type*. The patient died in May 1937.

A 28-year-old woman with *bilateral tuberculosis of the kidney*, which led to the patient's death about 4 years after the onset of the disease. Bovine T.B. were demonstrated in the urine. The source of infection was not traced.

*Case 34. Male, aged 25. Plumber, Hälsingborg.*

The father died from a cerebral haemorrhage in 1925, and the mother met with a fatal accident in 1914. In 1914 the patient moved from the

parish of Källua to Hälsingborg. From 1925 to 1930 he was employed as errand-boy, and from 1930 to 1933 as driver of a butcher's delivery van. In 1934, after completing his military service, he was at a labour camp. Since 1935 he has been employed as plumber at Hälsingborg. The source of infection was not discovered.

In May 1936 the patient had a *pain in the left side of the abdomen*, which radiated towards the back, not downwards. No urinary symptoms. The tuberculin reaction was positive and the rate of sedimentation 41 mm. The examination of the urine showed the presence of aseptic pyuria. *Bovine tubercle bacilli were found in the urine*. Radiographic examination of the lungs showed residues of a healed left-sided primary complex (calcifications), but otherwise nothing abnormal. The radiogram of the abdomen revealed no signs of calcified lymph nodes. The subsequent examination showed the presence of a bilateral renal tuberculosis. Left-sided nephrectomy was performed in 1938. The entire kidney was interspersed with cavities, containing caseous matter, up to the size of Spanish nuts. Further, both old and fresh changes could be seen in the kidney. Tuberculous ulcerations were found in the left ureter.

A 25-year-old man with *bilateral tuberculosis of the kidney and signs (calcifications) of an earlier tuberculous affection of the hilum and the lung (primary complex)*. Bovine T.B. in the urine. The patient's health is at present good. The source of infection was not traced.

*Case 35. Male, aged 34. Taxi-driver, Lund.*

A sister died of pulmonary tuberculosis in 1925. The parents and other children in good health. The patient was born in Lund but spent the first 18 years of his life in the country outside the city, where he came into contact with cattle and drank raw milk. He did not milk cows. It is not known whether tuberculosis occurred among the cattle. At the age of 18 he moved to Gothenburg, but returned to Lund in 1925. The source of infection has not been found.

About 3—4 years ago the patient had for a short time *gastric trouble after eating*. He was then well until the summer of 1937, when he felt *fatigued and lost his appetite*. At Christmas-time he developed a *cough*, had a *stitch in the right side of the chest* and *fever*. The pain in the chest recurred at intervals later. During the spring and summer of 1938 the patient was admitted on three different occasions to a hospital. He was then tuberculin positive, and the rate of sedimentation was greatly increased (96 mm on the first admission). The abdominal radiogram showed abundant calcified lymph nodes in the median line all the way from TII<sub>XII</sub> down to the central part of the sacrum. The radiograms of the lungs were normal, without any evidence (calcifications, etc.) of a previous tuberculous infection. The right renal shadow was greatly enlarged, with a well-defined,

round swelling, fully as large as a man's fist, in the upper part. The subsequent examination established the diagnosis of a right-sided renal tuberculosis. Nephrectomy was performed in May 1938. The kidney was large and pyonephrotic. The sac was made up partly of caseous granulation tissue, containing tubercles. *Pus from the sac was found to contain bovine tubercle bacilli.* The patient is at present well and is fully capable of working.

A 34-year-old man with signs of an *old tuberculosis of the abdominal nodes* and a *fresh right-sided renal tuberculosis*. Bovine T.B. were found in pus from a pyonephrotic sac. The patient's present health is good. The source of infection was not found.

*Case 36.* Female, aged 34. Microscopist, Hörby.

Parents and other children of the family healthy. Since 1922 the patient has been employed as microscopist at the Hörby slaughter-house, where she naturally came into contact with bovine tuberculous material. She generally obtained milk (pasteurised) from a dairy, but during certain periods procured it from farms in the vicinity. The source of infection has not been traced (the slaughter-house?).

On several occasions the patient was troubled with a *severe cystitis*. For that reason she was admitted to hospital for observation in October 1938. She was then tuberculin positive and had a sedimentation rate of 50 mm. Aseptic pyuria was diagnosed. Intravenous pyelography showed nothing abnormal on the right side, but on the left side the contrast filling of the renal pelvis was greatly delayed. The abdominal radiogram revealed calcified lymph nodes. On the other hand, the radiograms of the lungs showed normal conditions, no evidence (calcifications, etc.) of a previous tuberculous infection being seen. The subsequent examination disclosed the presence of a left-sided renal tuberculosis. *The tubercle bacilli present in the urine were of bovine type.* Left-sided nephrectomy was performed in January 1939. The kidney was interspersed with cystic, tuberculous cavities. The patient is at present remarkably well and is able to carry on her work.

A 34-year-old woman with signs of an *old tuberculosis of the abdominal nodes* and a *fresh left-sided renal tuberculosis*. Bovine T.B. were demonstrated in the urine. The patient's present health is good. The source of infection was not discovered (the slaughter-house?).

*Case 37.* Male, aged 25. Farm-labourer, Järrestad.

The family is healthy and without any evidence of tuberculosis. The patient has been employed as labourer at different farms, where he also milked cows and consumed raw milk. It is not known whether tuber-

culosis occurred among the cattle. No veterinary inspection was made. The source of infection has not been traced.

In June 1937 the patient had a *right-sided renal colic* and *bladder trouble*. The symptoms recurred at short intervals. The examination disclosed that he was tuberculin positive and that the rate of sedimentation was only 3 mm. The radiograms of the lungs were normal, without any signs (calcifications, etc.) of a previous tuberculous infection. *The urine contained abundant pus cells and, when typed, the tubercle bacilli were found to be bovine.* The subsequent examination revealed the presence of a right-sided renal tuberculosis. Nephrectomy was not performed until January 1938. In about the middle of the kidney there was an almost infarct-like area about the size of a hazel-nut, containing dense, partly caseous, miliary nodules. Solitary tuberculous nodules were also met with in the right ureter. The patient is at present well.

A 25-year-old man with *right-sided renal tuberculosis*. Bovine T.B. in the urine. The patient's present health is good. The source of infection was not found.

*Case 38.* Male, aged 32. Building-trade operative, Nordanå.

The parents died at an advanced age (not tuberculosis); a brother died in childhood of hip-joint tuberculosis. Otherwise the family is in good health, without any evidence of tuberculosis. The patient has always lived in the village of Nordanå. Up to 1927 he worked as a farm-labourer (also milked and drank raw milk), since then he has been employed as a building-trade operative. The source of infection has not been traced.

In 1916 the patient had a left-sided exudative pleurisy. In April 1934 epididymit. et vesiculit. seminal. dx. tbc. (and tbc. renis dx.?) was diagnosed. To a tuberculin test made now for the first time he gave a positive reaction. The rate of sedimentation was 18 mm. The radiographic examination of the lungs revealed, in addition to a left-sided pleuritic residue, also large calcified spots in the left superclavicular region, but no calcifications in the hilar regions. In June 1934 ablation of the right testis was performed. In the following year the patient developed tuberculosis of the left epididymis, which necessitated epididymectomy. In August 1935 aseptic pyuria was diagnosed. Tubercle bacilli were found in the urine. Guinea-pig tests with urine from both kidneys gave positive results in March 1936. Diabetes mellitus and right-sided exudative pleurisy developed in April 1937. Inoculations of the pleural fluid into guinea-pigs gave negative results. *The bacilli present in the urine were typed and found to be bovine.* A re-examination in December 1939 gave the same result. An X-ray examination of the abdomen did not reveal any calcifications. The cervical lymph nodes were normal. The patient's present condition is astonishingly good.

A 32-year-old man with healed *residues of an earlier tuberculous process in the left apical field*. Later the patient, in addition to diabetes mellitus, showed one tuberculous manifestation after the other (in 1916 *left-sided exudative pleurisy*, in 1934 *right-sided epididymitis and tuberculosis of the right seminal vesicle*, in 1935 *left-sided epididymitis and bilateral renal tuberculosis*, in 1937 *right-sided exudative pleurisy*). The patient's condition is nevertheless surprisingly good. Bovine T.B. in the urine. The source of infection was not found.

*Case 39.* Female, aged 18. Domestic servant, Malmö. (Father, farmer, Kulladal).

Parents and other children of the family in good health. Until the age of 14 the patient lived in the country. During 1930—1933 she was employed as domestic servant at different places, mostly in Malmö, and later, up to June 1934, at different farms. She often drank raw milk, but never had anything to do with tending cattle or milking. No information is available as to whether tuberculosis occurred among the cattle on these farms. The source of infection could not be traced.

In May 1935 the patient had *erythema nodosum*. After an intervening period of good health she again became ill in March 1937. She felt more and more *fatigued* and had a *fever*. On examination she was found to be affected with a right-sided pulmonary tuberculosis. The radiograms showed a mottled density within  $Scl-I_{II}$ , which laterally in  $I_{II}$  coalesced into a spot hardly as large as a hazel-nut. On the other hand, no evidence of a previous primary complex was discernible. No tubercle bacilli were found in the sputum or in the stomach washing. An X-ray examination of the abdomen revealed no abnormalities. The lymph nodes of the neck were normal. The lung changes have since progressed a little, but are still non-bacillary. In 1938 aseptic pyuria was diagnosed. The subsequent examination gave the diagnosis of right-sided renal tuberculosis. The sedimentation rate was 21 mm. *Bovine tubercle bacilli were found in the urine*. In spite of the fact that no operation has yet been performed the patient's health is good.

An 18-year-old woman who, at the age of 16 years, had *erythema nodosum*. Two years later she had *pulmonary tuberculosis and renal tuberculosis*. Bovine T.B. were found in the urine. The patient's health is at present good. The source of infection was not discovered.

*Case 40.* Male, aged 68. Farmer, Rynge.

The parents died of decrepitude. The patient's wife shows evidence of a healed pulmonary tuberculosis. There are no children, nor any brothers

or sisters. Until about 15 years ago the patient was a stone-cutter, then he procured a small farm, but about a year ago he let it. No bovine tuberculosis is said to have occurred on the farm. The source of infection was not traced.

For the past year (1937) the patient has felt *fatigued* and *lost very much weight* (about 20 kilos). Six months ago he began to complain of a *severe thirst*. Diabetes mellitus was diagnosed in July 1938. On account of a feeling of *unsteadiness on his legs* and *dyspnoea* he was admitted to hospital in August the same year. He was then tuberculin positive and had a sedimentation rate of 52 mm. No enlarged lymph nodes occurred on the neck. X-ray examination of the lungs revealed seemingly rather slight changes. In the centre of the left lung field there was a slightly striated and somewhat mottled opacity about the size of the palm of a man's hand, and behind the right C<sub>5</sub> a cloudy spot scarcely as large as a walnut with a central rarefaction (cavity) (Fig. 11). No evidence of a previous primary complex could be seen in the regions of the lungs and hili. *Bovine tubercle bacilli* occurred abundantly in the sputum. The patient's general condition became gradually worse, probably due chiefly to the diabetes, and he died in February 1939. As the patient was too weak to return for a control examination, no records are available of the development of the pulmonary tuberculosis during the last six months of life. There was no necropsy.

A 68-year-old man with *diabetes mellitus* and *bilateral tuberculous changes*, at first relatively benign, in the lungs (a small cavity). Bovine T.B. in the sputum. *Death took place about 6 months after the establishment of the diagnosis*, probably due chiefly to the diabetes. The source of infection was not discovered.

*Case 41. Male, aged 40. Textile worker, Farulund.*

The mother died of pneumonia at the age of 60, and a brother after a renal operation at the age of 40. Otherwise the family is healthy and without any evidence of tuberculosis. Milk was obtained from the village milk-shop, which received its supplies from a farm with a non-reactive herd. The milk was not pasteurised. The patient had not milked or tended cattle. No veterinary inspection had been made. The source of infection was not traced.

In March 1938 the patient became *hoarse* and *began to cough*. The cough became gradually worse; abundant yellowish *sputum* was present. The following month he developed *fever*, had *night sweats*, *loss of appetite* and *wasting*. An examination showed that he was tuberculin positive and had a sedimentation rate of 35 mm. No enlarged lymph nodes appeared on the neck. Radiograms of the lungs revealed a mottled density and pleural coating in both apical fields. The changes were somewhat more pronounced on the right side. At the base of the left lung — close

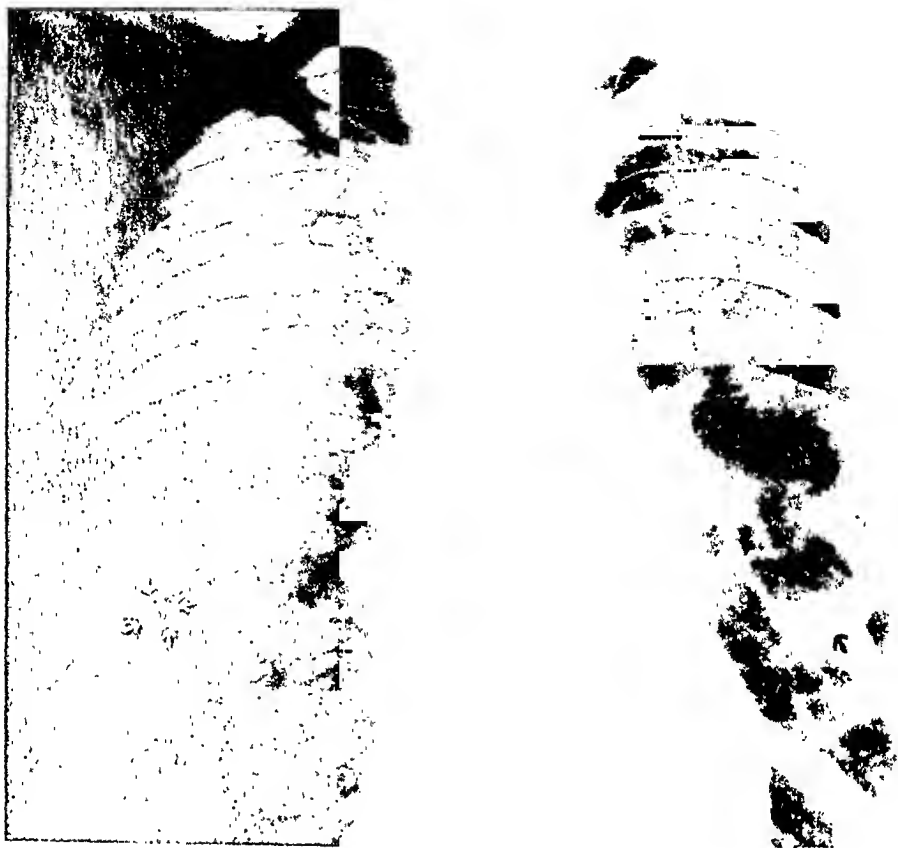


Fig. 11.

*Case 40.* A farmer aged 68 with *diabetes mellitus* and *bilateral pulmonary tuberculosis*. When the diagnosis was made (see above) there appeared in the left lung field a sparse, striated, partly mottled shadow, and behind the right C, a cloudy spot, barely the size of a walnut, with central rarefaction (a cavity). *Bovine tubercle bacilli* were found abundantly in the sputum. The patient died about 6 months after the diagnosis of the pulmonary affection.

to the apex of the heart — there was also a mottled shadow. No residues of a previous primary infection could be observed (Fig. 12). *Abundant bovine tubercle bacilli* were found in the sputum. The basal changes have gradually disappeared altogether, while only small residues remain of the apical changes. The patient is at present doing well and is able to work.

A 40-year-old man with *bilateral, rather benign bovine pulmonary tuberculosis*, which has undergone regression. *Bovine T.B.* in the sputum. The patient's present health is good. The source of infection was not discovered.

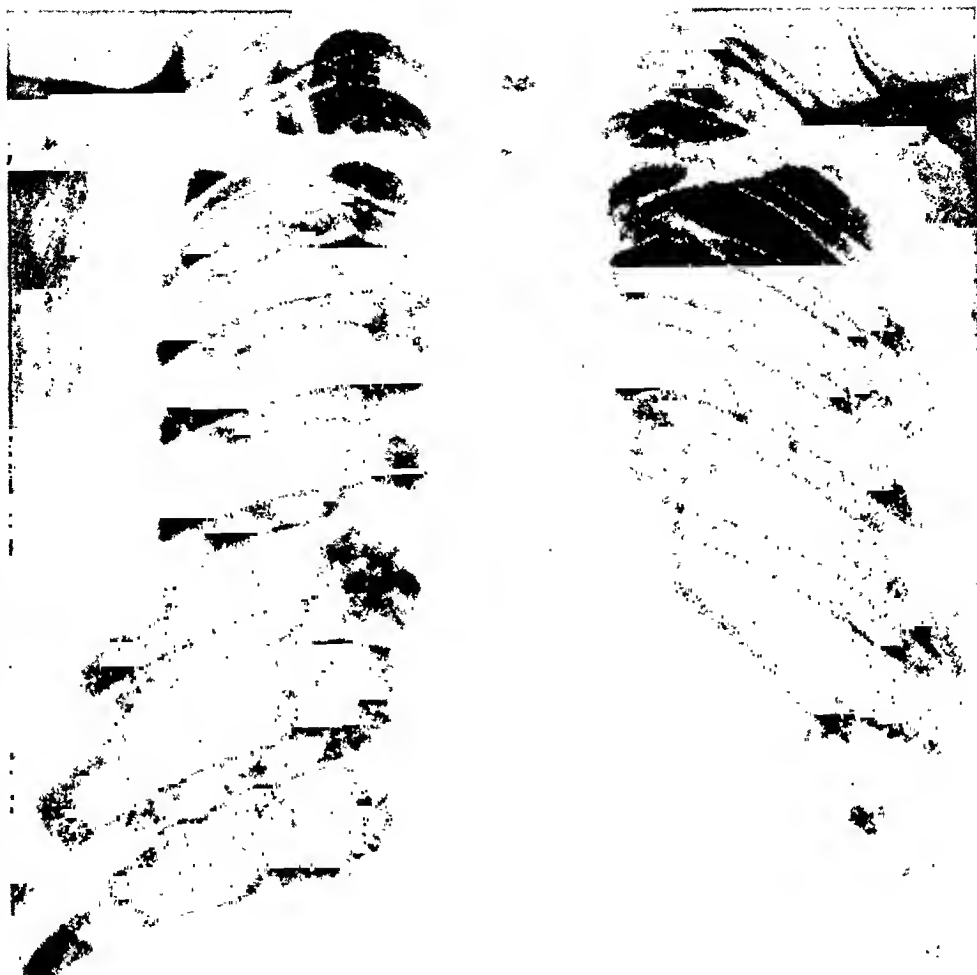


Fig. 12.

*Case 11.* A 10-year-old textile worker with *bilateral pulmonary tuberculosis*. The picture shows the condition when the disease was diagnosed. In both apical fields there was a mottled opacity and pleural coating, not very clear in the picture. A corresponding change was also discernible at the base of the left lung. *Bovine tubercle bacilli* were abundantly present in the sputum. The changes have since regressed. The present health is good.

*Case 12.* Male, aged 23. Cowman, Lödölesborg.

An aunt has had an exudative pleurisy, but is now in good health. The father died of pulmonary tuberculosis (bilateral, cavernous phthisis; the bacteria were not typed) in 1925. A sister had pulmonary tuberculosis of *human* origin in 1933. The mother and the other children of the family are in good health.

The patient has seldom met his tuberculous sister. He has been employed as cowman at different farms. Bovine tuberculosis occasionally



occurred among the cattle he came in contact with. He has milked and also consumed raw milk.

On account of the sister's illness the patient was examined in 1933, but no tuberculous changes could be observed (the X-ray examination was also negative). In the beginning of October 1937 the patient complained of *headache, cold in the head and cough*. The two first-mentioned symptoms soon disappeared, but the cough obstinately remained. In November he had *haemoptysis*, which necessitated admission to hospital. He was then tuberculin positive and had a sedimentation rate of 6 mm. The cervical lymph nodes were not enlarged. The radiographic examination revealed a cloudy opacity with a rarefaction the size of a cherry (probably a small cavity, see Fig. 13) in the right supraclavicular region. Otherwise the lung fields were entirely normal. No calcifications suggestive of an earlier primary lesion could be observed in the areas of the lungs and hili. Nor did the radiography of the abdomen show any calcified lymph nodes. *Bovine tubercle bacilli were sparsely found in the sputum*. The patient received sanatorium care. The changes underwent a slow regression. Only very small residues remain at present. The patient feels well and is able to work full time.

A 23-year-old man with *right-sided pulmonary tuberculosis (a fresh cavity)*, which regressed later. Bovine T.B. in the sputum. The patient's health is at present good. The source of infection was not traced.

*Case 43.* Male, aged 16. Farm-labourer, Osbyholm. (Father, tenant-farmer).

The parents and two of the children in good health. A sister of the patient had erythema nodosum in 1939 but did not either then or later show any other signs of tuberculosis. The patient, who was born and brought up in the country, has tended cattle and milked cows. He has also consumed raw milk. The veterinary inspection indicated that the patient could not have been infected by the cows belonging to the farm. He may have transmitted the disease to the sister who had erythema nodosum. The source of infection was not detected.

Owing to his sister's illness the patient was examined in March 1939. Although he had *felt quite well all the time* an X-ray examination revealed the presence of a cloudy shadow, nearly as large as a walnut, medially in the left I<sub>11</sub>. The left hilar region was somewhat enlarged and condensed. Striated opacities occurred in the left I<sub>1</sub>—I<sub>11</sub>. No signs of an earlier primary tuberculous infection could be observed. No cervical node tuberculosis occurred. The patient was tuberculin positive and had a sedimentation rate of 26 mm. *Bovine tubercle bacilli were demonstrated in the gastric lavage*. The changes have since regressed. The patient's present health is good.



Fig. 13.

*Case 42.* A cowman, aged 23, with *right-sided pulmonary tuberculosis*. The picture shows the appearance of the lesions when the disease was diagnosed. In the right supraclavicular region there was a cloudy opacity, in the centre of which there occurred a rarefaction as large as a cherry (probably a small cavity). *Bovine tubercle bacilli* were sparingly found in the sputum. The changes have since undergone regression. The present health is good.

A 16-year-old youth with *left-sided pulmonary tuberculosis*, which later regressed. Bovine T.B. in the gastric lavage. His health is at present good. The source of infection was not discovered.

*Case 44.* Female, aged 26. Typist, Limhamn.

The father is in good health. The mother died of pericarditis. A brother died of pulmonary tuberculosis (unfortunately the bacteria were not typed) in 1938. The source of infection was not found. The patient has not been in contact with cattle, has not milked or, as far as she is aware, consumed raw milk.

The patient felt quite well until October 1934, when she began to *cough* and gradually also to *expectorate*. Otherwise she felt in good health and carried on her work as usual. The cough persisted, but did not give occasion



Fig. 14.

*Case 44.* An unmarried woman aged 26 years, typist, with *bilateral pulmonary tuberculosis*. When the affection was diagnosed (see above) there were mottled, cloudy changes with bronchiectasis in the right ScI—I<sub>III</sub> and small spots and striated shadows in the left ScI—I<sub>I</sub>. *Bovine tubercle bacilli* were abundantly present in the sputum. In spite of bilateral pneumothorax treatment the changes have lately progressed. The condition must now be regarded as hopeless.

for an examination until January 1939, when a bilateral pulmonary tuberculosis was diagnosed. *Abundant bovine tubercle bacilli* were present in the sputum. The patient was tuberculin positive and showed a sedimentation rate of 82 mm. No tuberculosis of the cervical nodes could be found nor any evidence of a previous tuberculous infection in the regions of the lungs and hili. The radiographic examination revealed mottled, cloudy changes with bronchiectasis within the right ScI—I<sub>III</sub>; small spots and

striated shadows were also seen within the left ScI—I<sub>I</sub> (Fig. 14). Right-sided pneumothorax was at once induced, but was only temporarily effective as the upper part of the lung adhered to the chest wall and could not be divided by cauterisation. The patient's general condition at first improved, the rate of sedimentation fell and she increased in weight. But already in March the same year a right-sided exudation developed, which brought about fever and an increasing deterioration of the general condition. Left-sided pneumothorax was induced in September 1939. But here, too, the collapse of the lung was incomplete. Serious haemoptyses occurred. Since then the condition has gradually grown worse and is now absolutely hopeless.

A 26-year-old woman with extensive *bilateral pulmonary tuberculosis* (no cavitation), which despite pneumothorax treatment on both sides has steadily progressed. The condition is hopeless. Bovine T.B. in the sputum. The source of infection has not been found (the brother?).

*Case 15.* Male, aged 40. Cowman, Klagshamn.

The parents died at an advanced age (not from tuberculosis). The patient's brothers and sisters, his wife and children are healthy. Two nephews have pulmonary tuberculosis (human tubercle bacilli). From 1910 to 1929 (14—33 years old) the patient was employed as labourer at different farms. He afterwards worked at a lime-stone quarry until 1936 and since then he has been employed as cowman at a farm outside the village of Klagshamn. He has milked cows and consumed raw milk. No bovine tuberculosis is said to have occurred at the last-mentioned farm. The animals, however, are tuberculin reactors. No veterinary inspection was made. The source of infection has not been established.

In October 1936 the patient began to *feel tired* and *lost his appetite*. In November he had a troublesome *dry cough* and *dyspnoea*, shortly afterwards also *fever*. His condition became worse during the following weeks, *sputum* became gradually more abundant, and he *lost* about 10 kilos in *weight*. For this reason he was admitted to hospital, and on examination was found to have a bilateral exudative pleurisy. Repeated thoracenteses were performed. *Bovine tubercle bacilli* were found in the exudate. The patient was now tuberculin positive and had a sedimentation rate of 71 mm. The temperature remained constant between 39° and 40° C, and fell very slowly later; it did not return to normal until August 1937. The radiographic examination of the lungs at first showed nothing abnormal and did not reveal any evidence (calcifications, etc.) of a previous primary tuberculous infection. X-ray examination of the abdomen showed no nodular calcifications. The liver was evidently enlarged, its margin reaching to the crest of the ileum. The spleen, too, was enlarged. Ascites could not be established. In August 1937 a dense, mottled parenchymal density appear-

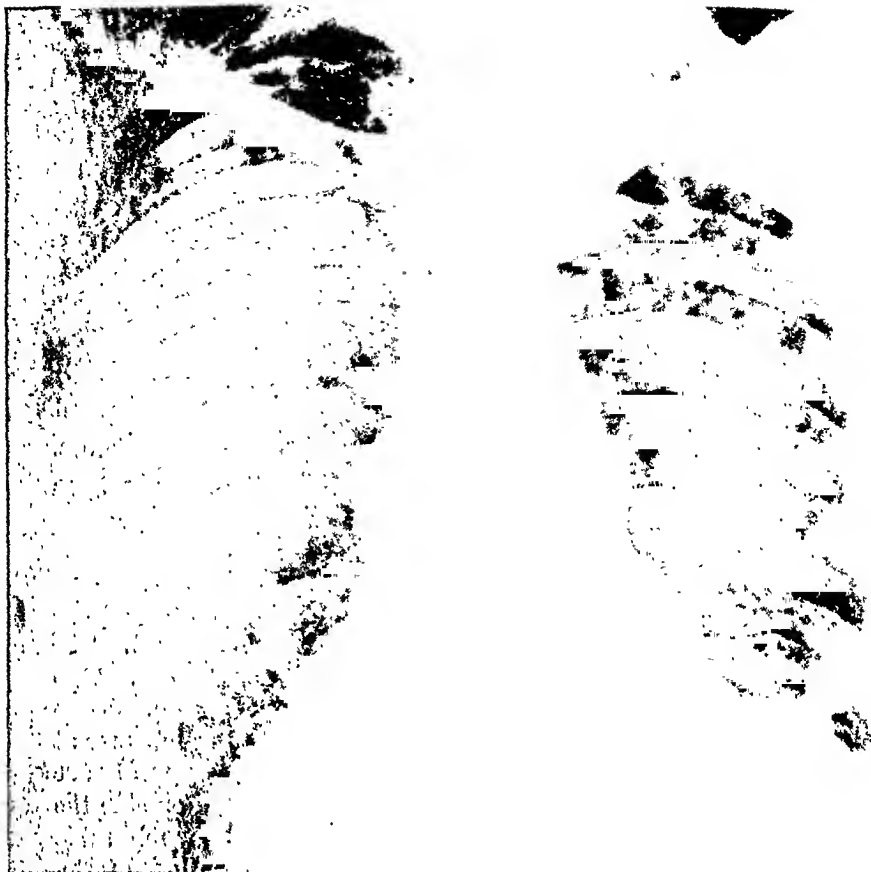


Fig. 15.

*Case 45.* A 40-year-old cowman, who one year previously had *bilateral bovine pleurisy*, now has *bilateral bovine pulmonary tuberculosis* of a haematogenous type. The picture shows the appearance of the lungs at the onset of the pulmonary changes. In the upper one-third of both lungs can be seen a dense, mottled parenchymal density; rests of earlier exudative pleurisy are also discernible. *Bovine tubercle bacilli* were found in the pleural exudate and in the sputum. The lung changes progressed at first, but have remained stationary for the last three years. The patient's present health is relatively good.

ed in the upper one-third of both lungs (Fig. 15). The rate of sedimentation was now 21 mm. The changes progressed slowly, but have remained stationary for the past year or two. No cavitation. The tuberculous lung process still presents a mottled picture. *Bovine tubercle bacilli* were sparingly present in the sputum. The general condition is at present fairly good but the patient is unable to work.

A 40-year-old man with *bilateral bovine tuberculous pleurisy* and a greatly affected general condition (high fever, considerable



Fig. 16.

*Case 46.* A farm-labourer of 18 years with *tuberculosis of bones and bilateral pulmonary tuberculosis* (scrofulosis 5 years previously). The appearance of the lung changes at the time of the diagnosis is shown in the picture. A pleural condensation can be observed in the right sinus, extending up along the thoracic wall. Slight parenchymal changes (hardly visible in the picture) occurred in the right upper field, and in the left supraclavicular region there was a cloudy shadow, about an inch in size. *Bovine tubercle bacilli* were shown in the gastric lavage. The changes have since regressed. The present health is good.

enlargement of the liver and moderate enlargement of the spleen). About a year later he had *bilateral bovine phthisis of a haematogenous type*. Bovine T.B. were demonstrated in the pleural exudate and in the sputum. The patient's present health is fairly good. The source of infection was not discovered.

*Case 46.* Male, aged 18. Farm-labourer, Svalöv.

The parents are healthy. A sister died of an unknown disease at an early age. The other children of the family are healthy and do not show any signs of tuberculosis. The patient was born and brought up in the country. Since the age of 14 he has been employed at different farms. It is not known whether he came into contact with bovine tuberculosis during this time. The source of infection could not be traced.

In 1930 (when he was 13 years old) the patient had *»scrofula* of the eyes, for which he received a few months' treatment at a seaside sanatorium. He was afterwards in good health until August 1935, when he began to complain of *pain in the right ankle-joint*. In January 1936 tuberculosis of the right foot was diagnosed. He was now tuberculin positive and had a sedimentation rate of 47 mm. Radiograms of the lungs revealed also bilateral pulmonary tuberculosis (Fig. 16). In the right sinus there was a pleural condensation, extending up along the wall of the chest. In the right upper field there were slight parenchymal changes, hardly visible in the picture. A striated density extended up towards a cloudy shadow, about an inch in size, in the left supraclavicular region. A slight diffuse opacity could also be seen within a limited area in the centre of the left lung. On the other hand, no signs of a previous primary infection could be observed. The cervical lymph nodes were normal. During the subsequent treatment the changes have slowly regressed. *Bovine tubercle bacilli* were found in the gastric lavage in 1936. The patient's present health is good.

An 18-year-old youth, who had had *scrofulosis* when 13 years old, developed *tuberculosis of the right foot and bilateral pulmonary tuberculosis* 5 years later. The lung changes gradually regressed. Bovine T.B. in the gastric lavage. His present condition is good. The source of infection was not found.

*Case 47.* Female, aged 17. Shop-assistant, Lund.

The mother died of pulmonary tuberculosis in 1927. The rest of the family is healthy and without any signs of tuberculosis. For the past 5 years the patient, who was born and brought up in the country, has been living in the city of Lund. The father formerly had a farm with a herd of 3-4 cows. As far as is known, no tuberculosis occurred among the animals. The patient has not milked but she has consumed raw milk. The source of infection has not been traced.

When 9 years old (in 1928) the patient was admitted to hospital on account of suspected pulmonary tuberculosis. No tubercle bacilli could be found. In August 1936 she had a *cough* and rather abundant *expectoration*. *Fever* and *increasing lassitude* soon set in. In September a right-sided pulmonary tuberculosis was diagnosed. Behind  $C_1$  and in  $I_1$  there was a cloudy opacity covering an area about the size of the palm of a man's hand with a rarefaction in the centre of this area. On the left side a pleural



Fig. 17.

*Case 47.* A 17-year-old female (shop-assistant) with bilateral *pulmonary tuberculosis*. The picture shows the condition when the disease was diagnosed. Behind  $C_1$  and in  $I_1$  there was a cloudy opacity with central rarefaction (cavity); on the left side a pleural thickening could be observed, also calcified spots in the hilum. After a week parenchymal changes appeared at the base of the left lung. *Bovine tubercle bacilli* were abundantly present in the sputum. The changes at first progressed, but regressed later following bilateral pneumothorax treatment. The health is at present good.

coating could be observed, also calcified spots in the hilum (Fig. 17). A week later spotty and striated parenchymal consolidation appeared at the base of the left lung. The tuberculin reaction was positive and the rate of sedimentation 30 mm. The lymph nodes of the neck were normal. *Abundant tubercle bacilli, which on typing were found to be bovine, were present in the sputum.* Shortly afterwards the left-sided changes showed progression and therefore pneumothorax was induced on that side. Already a month later artificial pneumothorax was induced also on the right side. Since then the bilateral pneumothorax treatment has been continued successfully. The patient has been non-bacillary for a long time; only small residues of the tuberculous changes now remain. The general condition is excellent and the patient is able to work. Radiographic



examination of the abdomen taken in May 1937 revealed no calcified nodes.

A 17-year-old girl who already at the age of 9 years had had suspected, but not absolutely verified pulmonary tuberculosis. Eight years later she had *bilateral pulmonary tuberculosis* (cavernous) and residues (calcifications) of an *earlier tuberculosis of the hilar glands*. Regression took place after bilateral pneumothorax treatment. Bovine T.B. in the sputum. The present condition is good. The source of infection was not detected.

*Case 48.* Female, aged 35. Husband, hospital-attendant, Ystad.

The family healthy. At the age of 15 the patient, who was born and brought up in the country, came to Lund as a nursemaid, where she remained for 3 years. Between 18 and 23 years of age she was employed as telephone operator at a small country village, and after getting married (at the age of 23) she has been living in the town of Ystad. She has never taken part in milking or tending cows. During childhood and while employed as telephone operator she drank raw milk. In recent years she drank pasteurised milk from a dairy. The source of infection has not been discovered.

In May—June 1931 the patient was treated for diabetes mellitus and again in November—December 1932 for diabetes mellitus and left-sided exudative pleurisy. The tuberculin reaction was positive and on admission the rate of sedimentation was 100 mm. but soon fell to 20 mm. The radiographic examination of the lungs revealed no pathological changes apart from the exudate shadow. On an insulin control examination in March 1939 a right-sided pulmonary tuberculosis was diagnosed. In the right upper lobe there now appeared a mottled, partly confluent density, most pronounced within C<sub>1</sub>—I<sub>II</sub>, also a residue of a left-sided pleurisy. (Fig. 18). Otherwise no evidence was discernible (calcifications, etc.) of a previous primary infection in the lung and hilar regions. The lymph nodes of the neck were normal; the rate of sedimentation was 25 mm. *Bovine tubercle bacilli were sparingly found in the sputum.* In April a right artificial pneumothorax was induced, which is still being kept up without complications. The lung is satisfactorily collapsed. Only small residue of the earlier changes can now be observed. The general condition is very good. The patient, however, is not yet able to work.

A 35-year-old woman who had had *diabetes mellitus* and a *left-sided exudative pleurisy* at 29 years of age. Six years later she developed *right-sided pulmonary tuberculosis*, which underwent regression after artificial pneumothorax treatment. Bovine T.B. were present in the sputum. The patient's present health is good. The source of infection was not found.

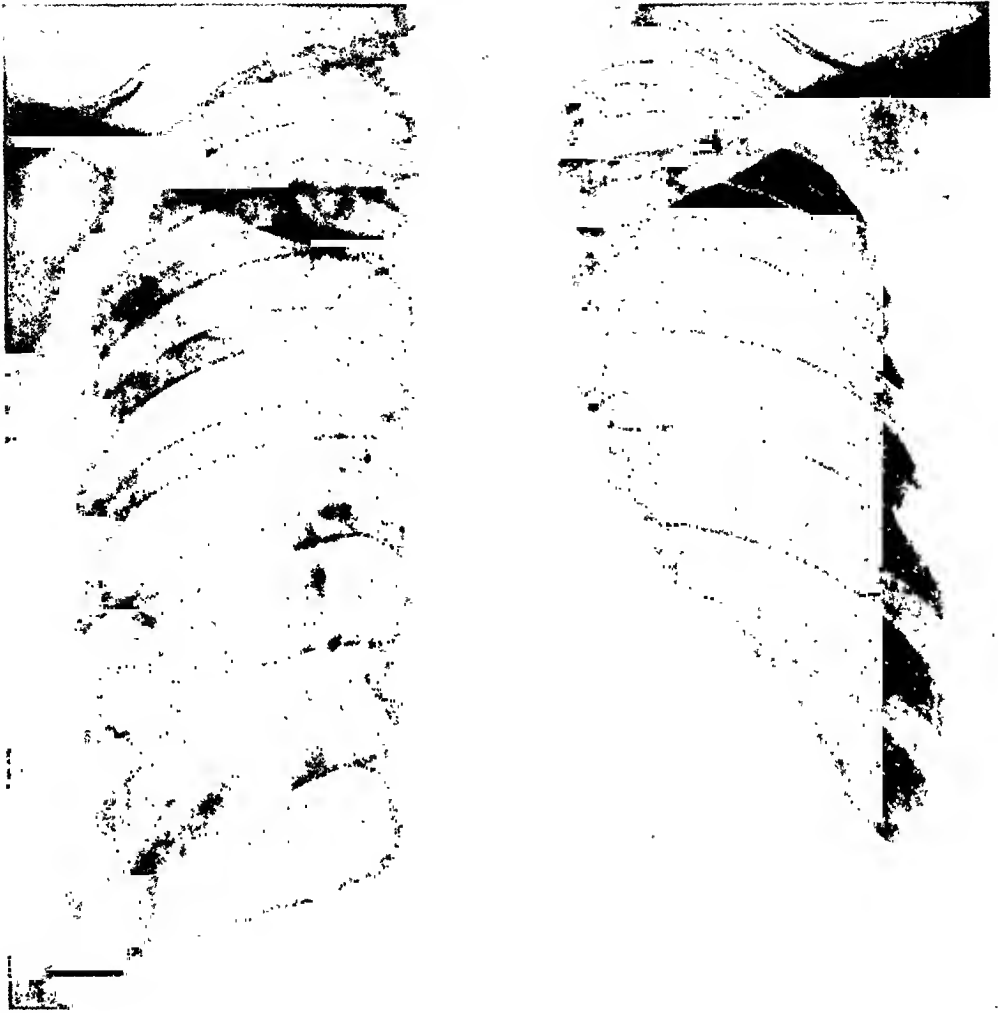


Fig. 18.

*Case 18.* A woman, aged 35 years, (wife of a hospital attendant) with *diabetes mellitus* and *right-sided pulmonary tuberculosis* (*left-sided exudative pleurisy* 6 years previously). The radiogram shows the appearance of the lung changes when the disease was diagnosed. In the right upper lobe is seen a mottled, partly confluent density, most pronounced within  $C_1 - III$ . Pleuritic rests can also be observed on the left side. *Bovine tubercle bacilli* occurred sparingly in the sputum. Regression took place after a right artificial pneumothorax. The health is at present good.

*Case 49.* Female, aged 21. Wife of a farmer, Lund.

In July 1938 a sister had erythema nodosum, left-sided hilar adenitis and left-sided pulmonary tuberculosis (primary complex) as the result of a bovine primary infection (Case 8). The parents and other children of the family are healthy. When examined in June 1938 the husband did not

show any signs of tuberculosis, but in the following month he had an exudative pleurisy (no tubercle bacilli were found and therefore no typing could be made). The patient sometimes lived with her parents in the country (the father is a farmer), at other times she was employed as servant at different farms until she got married in March 1938. The family has a small herd of 5 cows, purchased after marriage, which were then tuberculin non-reactive. It is noteworthy that one or two months later two of these cows gave a positive tuberculin reaction. No bovine tuberculosis occurred on the father's farm. It is not known to what extent the patient came into contact with tuberculous cows during her employment as domestic servant. She has consumed milk, also milked and tended cattle. The source of infection was not traced.

In 1934 the patient had *erythema nodosum*. The radiographic examination of the lungs then showed nothing abnormal. She was kept under regular supervision. In March 1938 she had persistent cough and scanty expectoration. The appetite was poor and she had lost weight. In May she complained of hoarseness, a stitch in the right side of the chest and tiredness. In June the same year, right-sided pulmonary tuberculosis was diagnosed. The rate of sedimentation was then 66 mm. Immediately outside the right hilar region there was a cavity as large as a plum. The lungs otherwise showed no signs of tuberculosis; no residues of a previous primary infection (calcifications, etc.) could be observed within the lung and hilar regions (Fig. 19). The cervical lymph nodes were normal. The sputum contained abundant bovine tubercle bacilli. A right artificial pneumothorax was induced at once and supplemented later with cauterisation of adhesions, which resulted in the collapse of the cavity. In August 1939 she had a right-sided pleurisy, which subsequently required oleothorax treatment. The general condition is a present good, but the patient is not yet able to work.

A 24-year-old woman who had *erythema nodosum* at 20 years of age. Four years later she had right-sided pulmonary tuberculosis (cavernous), which regressed after artificial pneumothorax treatment. Bovine T.B. were present in the sputum. When the patient became ill she was highly infective and transmitted the infection to a younger sister, who had a bovine primary complex in the left lung and hilar regions, and to her husband, who had a severe exudative pleurisy. Two of the five previously tuberculin negative cows belonging to the farm also became positive reactors. The patient's present health is good, but thoracentesis is occasionally necessary. The source of the infection could not be traced.

Case 50. Male, aged 47. Farm-labourer, Pårarp.

The family is healthy. The patient, who was born and brought up in the country, has been employed at different farms where cases of bovine

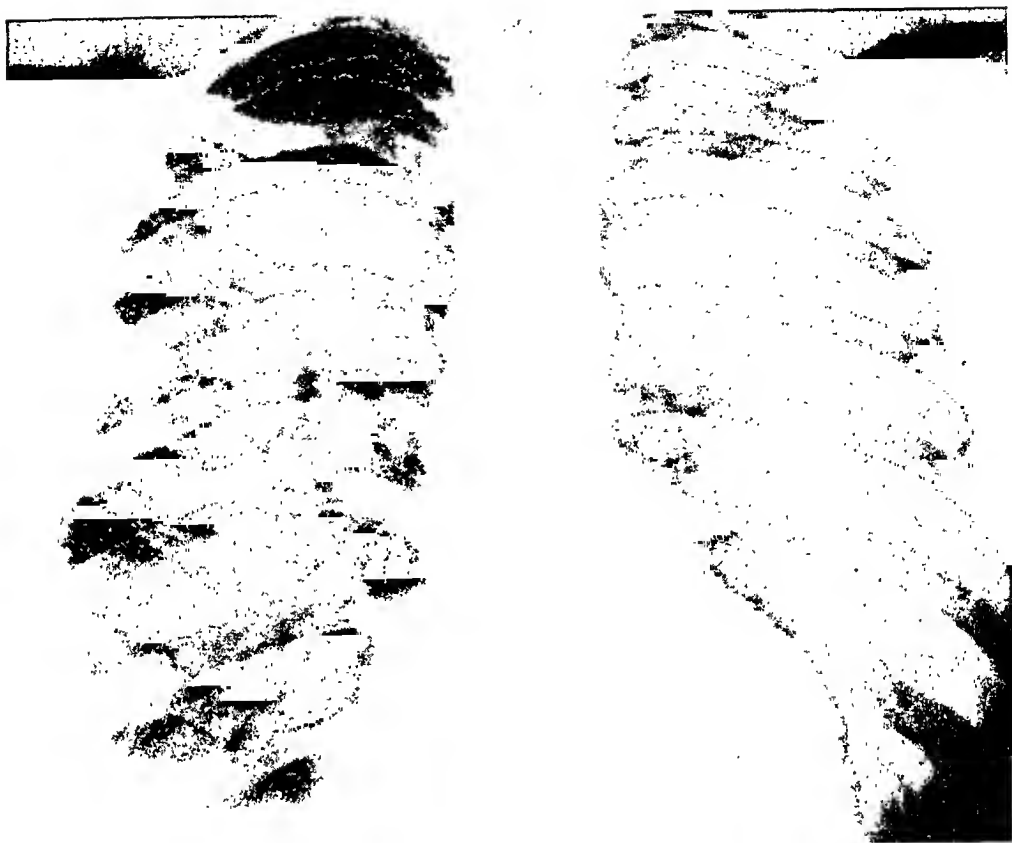


Fig. 19.

*Case 49.* A woman, aged 24, (wife of a farmer) with *right-sided pulmonary tuberculosis (erythema nodosum 4 years previously)*. The radiogram shows the condition of the lungs when the disease was diagnosed. The only change to be seen was a cavity as large as a plum immediately outside the right hilar region. *Abundant bovine tubercle bacilli were present in the sputum.* A right artificial pneumothorax and cauterisation of adhesions were performed. Later exudation appeared in the right pleura, which necessitated oleothorax treatment. The general condition is at present good. *The patient was probably the source of infection of Case 8 (Figs. 6—7).*

tuberculosis had previously occurred. He has not milked cows but has drunk raw milk. At his last situation, which he has had since 1933, the herd was tuberculin reactive. No veterinary examination was made. The source of infection was not discovered.

The patient felt quite well until 1935, when he began to complain of cough, especially in the morning. The cough became worse in 1938 and the



Fig. 20.

*Case 50.* A 47-year-old farm-labourer with *bilateral pulmonary tuberculosis*, resulting in *death* about 5 months after the diagnosing of the affection. The radiogram shows the pulmonary changes at the time the diagnosis was made. Tuberculous changes were found in the whole of the left lung, at the apex also an orange-sized cavity; less pronounced changes were present in the right lung. *Abundant tubercle bacilli* were found in the sputum.

patient now had a *poor appetite* and was *losing weight*. He also had occasional *night sweats*. He was nevertheless able to continue working until October of the same year, when the above-mentioned complaints and an *increasing fatigue* compelled him to consult a doctor, who diagnosed bilateral pulmonary tuberculosis. Extensive tuberculous changes were found in the entire left lung; an orange-sized cavity was also found at the apex. In the right lung the changes were less pronounced (Fig. 20). No evidence (calcification, etc.) of a previous primary infection were found in the areas

of the lungs and hili. The tuberculin reaction was positive and the rate of sedimentation 75 mm, the temperature, however, was normal. The cervical lymph nodes were normal. *Abundant bovine tubercle bacilli were found in the sputum.* The condition rapidly deteriorated and the patient died in March 1939. There was no necropsy.

A 47-year-old man with extensive *bilateral pulmonary tuberculosis* (a cavity the size of an orange). Death took place about 5 months after the disease had been diagnosed. Bovine T.B. were present in the sputum. The source of infection is not known.

*Case 51.* Female, aged 12. Father, farmer, Silvåkra.

The parents and the other children of the family are healthy. One or two cows have been kept on the farm on different occasions. As a rule the family consumed the raw milk produced by their own cows, but occasionally bought milk from neighbouring farms. No bovine tuberculosis is said to have occurred. The source of infection is not known.

The patient became acutely ill in April 1937, presenting *the picture of a right-sided pneumonia.* The temperature remained very high. In July the patient complained of *tiredness and cough.* She was not admitted to hospital until the following October, when a right-sided pulmonary tuberculosis was at once diagnosed. On admission the temperature was still high, 38°—39° C. The tuberculin reaction was positive, the rate of sedimentation 49 mm. The radiographic examination revealed a cloudy, spotty, mostly confluent parenchymal density in the upper two-thirds of the right lung. The right hilar shadow was considerably enlarged, in which could be seen a large calcified spot. Smaller calcified spots were also observed in the apex of the right lung. Small pleural striations were found in the left lung field (Fig. 21). *Bovine tubercle bacilli occurred regularly but rather sparingly in the sputum.* Radiography of the abdomen revealed no calcified nodes. The cervical lymph nodes were normal. A right artificial pneumothorax was induced at once, but was not effective. The tuberculous process spread irresistably down into the right lung and across to the left one. No abdominal symptoms occurred. After a long period of decline the patient died in August 1938.

The *necropsy* report by Dr. C. G. AHLSTRÖM was: The lung parenchyma on both sides was interspersed with pea- to hazel-nut-sized (acino-exudative and lobular caseous) foci showing a confluent tendency and central caseation, but without any discernible liquefaction. In both hili, in the mediastinum there were numerous caseous lymph nodes up to the size of hazelnuts. The larynx was normal. In the mesocoecum there was a number of bean-sized, softly elastic lymph nodes with a reddish brown, glossy cut surface, without any signs of caseation. Somewhat oval, transverse ulcerations, from the size of a three-penny-bit to that of a six-penny-bit, with soft, ridged edges, the surface of the ulcers coated with pus, were seen in

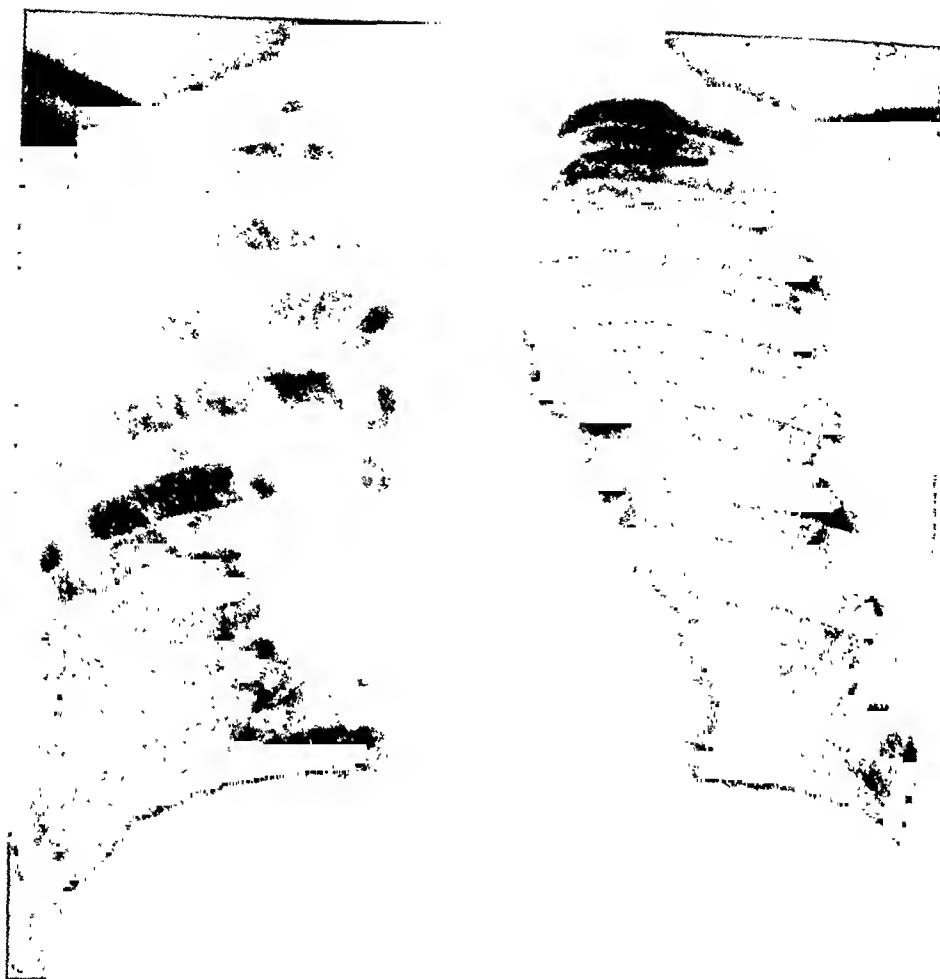


Fig. 21.

*Case 51.* A girl, aged 12 years, (father, farmer) with *right-sided pulmonary tuberculosis*, which caused her death about 11 months after the diagnosing of the disease, in spite of pneumothorax treatment. A cloudy, spotty, mostly confluent parenchymal density can be seen in the upper two-thirds of the right lung. The right hilar region appears to be considerably enlarged and consolidated, containing calcifications. *At the onset of the disease bovine tubercle bacilli sparingly occurred in the sputum.*

the coecum and the lower part of the ileum. On microscopic examination typical tuberculous foci with ulceration and necrosis were found in the wall of the ileum. The regionary glands of the mesentery contained miliary tuberculous foci.

The *necropsy diagnosis* was: Bilateral pulmonary tuberculosis, multiple tuberculous ulcers in the ileum and coecum. Caseous lymph node tuberculosis of the mediastinum.

A 12-year-old girl with *right-sided exudative pulmonary tuberculosis* and *signs of a previous hilar gland tuberculosis and pulmonary tuberculosis* (calcifications). Despite pneumothorax treatment the process irresistibly spread farther into the lungs, producing also disseminated *intestinal tuberculosis*. The patient died 11 months after the disease had been diagnosed. Bovine T.B. were demonstrated in the sputum and in the lung tissue (at necropsy). The source of infection could not be established.

*Case 52.* Female, aged 18. Dressmaker, Landskrona. Father, turner.

The parents and other children of the family in good health. A paternal aunt was treated for exudative pleurisy in 1933 but is now well. The patient occasionally met two phthisical persons. One of these persons is now dead and therefore no typing of the bacteria was possible; the other is affected with pulmonary tuberculosis due to *human* tubercle bacilli. For the last 8—10 years milk has been bought from a farm outside the town of Landskrona. A veterinary examination failed to find any infectious tuberculosis among the cattle. The source of infection was not traced.

In February 1935 the patient had tuberculous lymph nodes on the left side of the neck, which were surgically removed shortly afterwards. Radiograms of the lungs taken at that time showed nothing abnormal. In July 1936 new tuberculous lymphomata appeared, which were also excised. In December 1936 the patient had a troublesome *cough* and abundant *expectoration* and *fever*. She now also felt *tired* and occasionally had a *stitch in the left side of the chest*. Left-sided exudative pulmonary tuberculosis was diagnosed. The radiographic examination revealed a compact density in the lower half of the left lung. Further, the left hilar shadow was greatly enlarged and condensed. A calcified lymph node could be seen in the right hilar region and another smaller one projecting above the right supraclavicular area. Radiographic examination of the abdomen revealed the presence of numerous, large, calcified lymph nodes all the way from the pelvis inlet up to the 12th thoracic vertebra (Figs. 22—23). The tuberculin reaction was positive and the sedimentation rate 53 mm. Behind the left sternocleidomastoid muscle there were numerous painless lymph nodes, varying in size from a pea to a bean. In January 1937 the patient's condition deteriorated. The pneumonic area at the base of the left lung underwent liquefaction. In spite of pneumothorax treatment the cavity gradually increased so that in July it was as large as a plum. Now and then the patient felt a sensation of straining in the abdomen. The cervical lymph nodes also increased in size and by this time occupied the entire area between the left angle of the jaw and the supraclavicular fossa. The tuberculous process now spread also to the right lung. The temperature became high and hectic. After a protracted decline the patient died in September 1937. During the last days abdominal trouble developed,





Fig. 22.

*Case 52. An 18-year-old dressmaker (father, turner) with evidence of a very extensive, old tuberculosis of the abdominal nodes, of the right hilar region and of the neck, as well as a fresh, left-sided pulmonary tuberculosis. The picture shows the great abundance of calcified nodes in the abdomen. See also Fig. 23.*

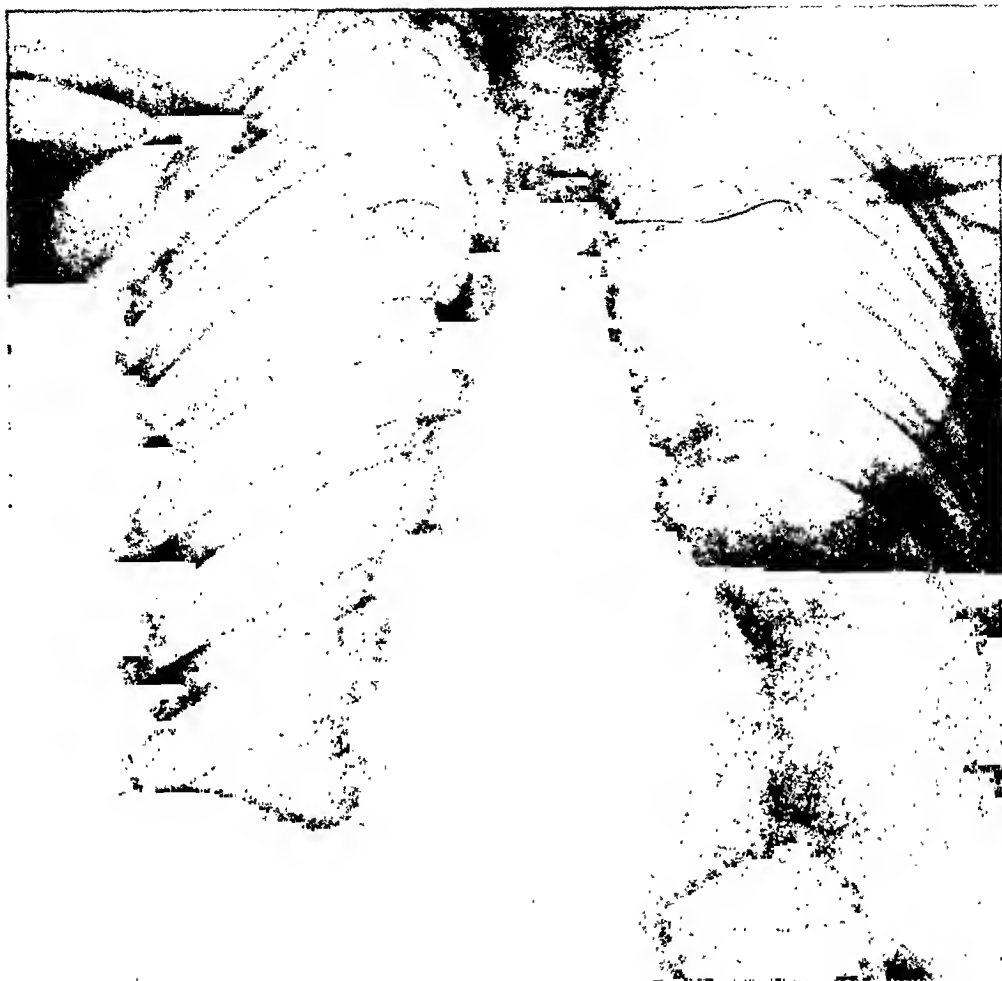


Fig. 23.

*Case 52.* (The same case as shown in Fig. 22). The picture shows the condition when the pulmonary changes were demonstrated. A compact consolidation due to exudative tuberculosis is seen in the lower half of the left lung. The left hilar shadow is enlarged and condensed. Calcified spots are seen in the right hilar region and in a lymph node on the right side of the neck (projecting above the right supraclavicular region). *Bovine tubercle bacilli* were abundantly present in the sputum and in different necropsy specimens. A cavity in the left lung developed rapidly. In spite of artificial pneumothorax death occurred about 9 months after the diagnosing of the pulmonary affection.

mostly in the form of diarrhoea. Repeated typings from the sputum and from various necropsy material showed the presence of abundant bovine tubercle bacilli.

The necropsy examination (performed by Dr. S. WINBLAD) gave the following result: . . . In the left hilum there was a large packet of caseous

lymph nodes varying in size from a hazel-nut to a walnut. Paratracheally on both sides there were large packets of nodes, which on the left side extended past the angle of the jaw up to the back of the ear. None of the nodes showed calcification or liquefaction. A packet of lymph nodes, as large as a walnut, with central calcifications, was seen in the right hilum. The lower part of the upper lobe of the left lung was transformed into an orange-sized cavity containing a small amount of caseous material. Moreover, the upper and lower lobes were interspersed with yellowish green tuberculous foci, partly acino-nodous, partly pea- to bean-sized cavities containing caseous matter. The lower lobe of the right lung showed centrally a tuberculous focus, the size of 2-shilling piece, without liquefaction or calcification. Otherwise the right lung was free from changes. No calcified primary complex was met with in this lung. The tonsils were small and without tuberculous changes. The peritoneal cavity contained 1,000 cm<sup>3</sup> of a yellowish brown, purulent fluid. The serosal surface of the intestines was reddened, especially in the lowest portion of the ileum, where two minute perforations could be observed. The distal portion of the ileum showed numerous crater-shaped ulcers, varying in size from a pin-head to a pea. In the proximal part of the coecum and colon there were pea-sized ulcers of the same appearance as those in the ileum. Greatly enlarged lymph nodes, fused into packets, were found along the vertebral column. A few of these lymph nodes were as large as plums, on section all of them were found to be caseous. Numerous enlarged lymph nodes were also met with in the mesentery. Thus, an *orange-sized packet of lymph nodes, partly so intensely calcified that they could be cut only with difficulty*, was found in the mesentery centrally to the ileocoecal region. In the portal region there was a packet of nodes as large as a man's fist. On macroscopic examination the spleen was found to contain necrotic tuberculous foci.

The *necropsy diagnosis* was: Tbc. prim. lfgl. mes. + tbc. lfgl. retroperitonealis et mediastinalis et paratrachealis et colli + tbc. acino-nodosa et cavernosa pulm. amb. + tbc. intestini tenui cum perforatione pur. + cystitis.

A girl of 18 with an *old glandular tuberculosis in the abdomen, in the right hilar region and on the neck*. In the first-mentioned locality the changes were very wide-spread (Fig. 22). After having had relapsing *tuberculosis of the cervical lymph nodes* for many years, which was treated surgically, the patient developed *left-sided exudative pulmonary tuberculosis* (Fig. 23), which despite pneumothorax treatment rapidly underwent cavitation and gradually spread to both lungs and to the intestines. Death took place after the perforation of intestinal tuberculous ulcers about 9 months after the pulmonary affection had been diagnosed. Bovine T.B.

were demonstrated in the sputum and necropsy material. The source of infection was not discovered.

*Case 53.* Female, aged 30. Unmarried. Photographer, Malmö.

The family is healthy and without any signs of tuberculosis. The patient has always lived in the city of Malmö. She is fond of milk. No known contact with tuberculous cattle. The source of infection was not traced.

The patient had tuberculosis of the cervical nodes in 1927. In January 1936 she had a *cough*, and shortly afterwards *fatigue*, *loss of weight* and a *high fever*. Bilateral pulmonary tuberculosis was diagnosed. In the upper one-third of the right lung there was a pneumonic consolidation with a central cavity the size of a hazel-nut. Cloudy spots could also be seen in the left apical and upper fields. No signs of a previous primary infection (calcifications, etc.) were discernible in the lung and hilar areas. On the other hand, the radiography of the abdomen revealed a number of small nodular calcifications on a level with the upper part of the sacrum. *Bovine tubercle bacilli* were abundantly present in the sputum. Right-sided artificial pneumothorax was induced almost immediately, but had to be broken off owing to an exudative pleurisy in the beginning of February 1937. Central progression in the left lung necessitated pneumothorax treatment also on that side in August 1936. The treatment is still being continued. The patient is able to work occasionally.

A woman of 30 with signs of *an old tuberculosis of the abdominal lymph nodes* and small residues of an earlier *tuberculosis of the cervical nodes*. After a symptomless interval of 9 years she again became ill with a *bilateral, exudative, pulmonary tuberculosis* (cavernous), which was somewhat improved by pneumothorax treatment. The patient's present health is relatively good. Bovine T.B. were demonstrated in the sputum. The source of infection was not traced.

*Case 54.* Male, aged 16, agricultural worker. Father, farmer, Skivarp.

Two cousins of the father died of pulmonary tuberculosis. The patient never met them. The family is otherwise healthy. The herd belonging to the farm consists of 12—14 cows and 30 pigs. Two pigs were slaughtered in 1933 and one cow in 1934 owing to their being affected with tuberculosis. The patient took part in milking and he has also drunk raw milk from the farm. The source of infection may therefore be regarded as established.

The patient, who was in complete subjective health, had an *haemoptysis* in April 1937. The subsequent examination revealed a bilateral exudative, cavernous phthisis. In the upper one-third of the left lung there was a confluent, cloudy opacity and a cavity as large as a hazel-nut on a level with C<sub>II</sub>. A striated density could also be seen in the right I<sub>1</sub> (Fig. 24).



Fig. 24.

*Case 54.* A 16-year-old agricultural worker (father, farmer) with *bilateral pulmonary tuberculosis*. The picture shows the condition at the time the affection was diagnosed. A confluent, cloudy density is seen in the upper one-third of the left lung, and a cavity the size of a hazel-nut appears on a level with C11. In the right lung only striated opacity can be seen at the right I<sub>1</sub>. *Bovine tubercle bacilli* were found abundantly in the sputum. Later a considerable progression took place in the right lung. After pneumothorax treatment, however, the condition is good.

On the other hand no evidence of an earlier primary infection (calcifications, etc.) could be shown in the lung and hilar regions or in the abdomen. *Bovine tubercle bacilli* were abundantly present in the sputum. The cervical lymph nodes were normal, and the rate of sedimentation was 36 mm. A left artificial pneumothorax was induced at once and is still being continued. In June 1937 a considerable progression took place in the right lung, which was then

entirely interspersed with rather large spots, but they disappeared again after a long period of sanatorium treatment. The condition greatly improved during the treatment.

A youth of 16 with an acute onset of exudative *bilateral pulmonary tuberculosis* (cavernous). Regression took place after a long period of pneumothorax treatment. The patient's present health is good but he is not yet fit for work. Bovine T.B. were present in the sputum. The source of infection is known.

*Case 55.* Male, aged 21. Painter, Landskrona.

Parents and brothers and sisters are healthy. The patient has always lived in the town of Landskrona with the exception of the spring of 1936, when he was away for 5 months at Karlskrona serving his time in the navy. The milk at Landskrona is pasteurised. The source of infection was not traced.

During the past 5 years the patient has had a «cold» and a cough with yellow, mucous sputum. In January 1937, in complete subjective health, he had a *haemoptysis*, which led to a thorough examination and the detection of a left-sided exudative pulmonary tuberculosis (cavernous). The radiographic examination of the lungs showed a confluent, cloudy density in the upper half of the left lung and a cavity almost as large as a walnut on a level with C<sub>II</sub> (Fig. 25). No evidence of an earlier primary infection (calcifications, etc.) could be observed in the lung and hilar regions, but on the other hand the radiography of the abdomen showed numerous glandular calcifications spread along the anterior aspect of the lumbar vertebrae, partly situated rather far in the abdomen. The tuberculin reaction was positive and the sedimentation rate 60 mm. The cervical lymph nodes were normal. *Abundant bovine tubercle bacilli were found in the sputum.* Pneumothorax treatment was instituted at once. At first the lung collapsed poorly, but after cauterisation of adhesions in April a satisfactory collapse was obtained. The cavity, however, showed no tendency to close. The general condition gradually deteriorated. Tuberculous lymph nodes appeared on the neck. Soon afterwards the tuberculous process spread over the right lung and the patient died on 15th August 1939.

The report of the *neeropsy examination* (performed by Dr. ALF SJÖVALL) was as follows: The cervical lymph nodes on both sides were enlarged, caseated, but nowhere liquefied. Enlarged tuberculous nodes extended from the neck along the large vessels in the median line of the body down into the pelvis. Caseous, yellowish white, round foci varying in size from a pea to a walnut were found in the right lung, especially in the middle lobe and the adjacent parts of the other two lobes. Similar changes were observed in the lower lobe of the left lung. No caseous degeneration or calcification was found in these areas. In the left upper lobe the picture was quite different. Here large, lobular, compact pneumonic changes were met



Fig. 25.

*Case 55. A man aged 21 years (painter) with evidence of an old tuberculosis of the abdominal lymph nodes and a fresh left-sided pulmonary tuberculosis. The picture shows the appearance of the pulmonary changes when the disease was diagnosed. A confluent, cloudy density is seen in the upper half of the left lung, and a cavity almost as large as a walnut on a level with CII. Bovine tubercle bacilli were abundantly present in the sputum. Died about 7 months later in spite of pneumothorax treatment.*

with. The most basal of these areas was entirely transformed into a whitish yellow caseous matter. No calcifications were met with in this lobe either. In addition to the lobular, caseous pneumonias there were also in the parenchyma, especially at the top, a number of tubercles of the same type as those in the right lung, but somewhat larger and surrounded by slate-coloured tissue, a few of the tubercles showing central disintegration. Caseation, however, was most pronounced around a walnut-sized cavity located about 2.5 cm from the apex. The hilar and mediastinal lymph nodes were enlarged, some of them as large as plums; they contained tuber-

culous caseous matter, which nowhere, however, showed liquefaction or calcification. In the ileum there were small, whitish grey, tuberculous nodules and, moreover, ulcers of varying forms from lenticular to the size of a threepenny piece, with uneven, excavated margins. The mesenteric lymph nodes were greatly swollen, and had fused into an enormous packet, which was connected with the aortic lymph nodes and extended in one solid mass over the entire posterior wall of the abdomen and for a long distance down into the right pelvis. On the cut surface the lymph nodes were caseated and surrounded by fibrous tissue. *Solitary mesenteric lymph nodes were calcified.* No degenerated or perforated lymph nodes were found anywhere.

The *necropsy diagnosis* was: Tbc. pulm. amb. c. pth. artif. sin. - tbc. hgl. colli mediastini et abd. + tbc. intestini.

A 21-year-old man with an *old tuberculosis of the abdominal lymph nodes* and a *left-sided exudative pulmonary tuberculosis* (cavernous). In spite of artificial pneumothorax treatment and cauterisation of adhesions the cavity could not be made to collapse. Tuberculous changes gradually appeared also in the right lung and in the cervical lymph nodes and later in the intestines. Death occurred about 7 months after the diagnosing of the pulmonary affection. Bovine T.B. were found in the sputum. The source of infection was not traced.

*Case 56.* Female, aged 25. Milkmaid, Snogeröd. Father, farmer.

The parents are in good health. A brother was treated for tuberculosis of the mediastinal and mesenteric lymph nodes in 1937. Guinea-pig tests with the gastric lavage were negative. He is at present quite well and is able to work. The patient's two children, 3 and 5 years respectively, gave a positive tuberculin reaction but otherwise showed no evidence of tuberculosis. The husband is healthy. The patient was employed as milkmaid at a farm where several cases of bovine tuberculosis in man have occurred (see Case 17). Thus a veterinary examination made in 1939 discovered open pulmonary tuberculosis in no less than 13 cows at the same time. The patient had milked and had also drunk raw milk from cows on this farm. The source of infection may therefore be regarded as established.

The patient began to cough in October 1936. She also felt tired, but kept on working as usual. When the symptoms increased she consulted a doctor in December the same year, when a left-sided, exudative, cavernous phthisis was diagnosed. A partly confluent, cloudy opacity was seen between C<sub>I</sub> and 1<sub>II</sub> and a walnut-sized cavity laterally in 1<sub>I</sub> (Fig. 26). No signs (calcifications, etc.) of an earlier primary tuberculous infection could be seen, however, within the lung and hilar regions nor in the abdo-





Fig. 26.

*Case 56.* A milkmaid aged 25 years (father, farmer) with *left-sided pulmonary tuberculosis*. The appearance of the lung changes at the time the affection was diagnosed is seen in the picture. Between C<sub>I</sub> and I<sub>II</sub> there is a partly confluent density, and laterally in I<sub>I</sub> a walnut-sized cavity (not quite so well marked in the picture). *Bovine tubercle bacilli* were found abundantly in the sputum. In spite of pneumothorax treatment the patient died about 17 months later.

men. *Bovine tubercle bacilli* were abundantly present in the sputum. The tuberculin reaction was positive and the sedimentation rate 24 mm. The lymph nodes of the neck were normal. A left artificial pneumothorax was induced in January 1937, but it was never effective owing to the lung being dilated by wide adhesions, which could not be cauterised. In order to try to get the cavity to collapse, an extrapleural pneumothorax was attempted in June 1937, but was soon complicated with empyema. This was gradually resorbed but the lung re-expanded. The cavity remained unaffected. The condition then gradually deteriorated, symptoms ultimately appearing indicative of intestinal tuberculosis. The patient died at her home in April 1938. There was no necropsy.

A woman of 25 with a *exudative, left-sided pulmonary tuberculosis* (cavernous). In spite of intrapleural and later extrapleural pneumothorax treatment the cavity did not close. The process subsequently spread also to the intestines. The patient died about 17 months after the disease had been diagnosed. Bovine T.B. were demonstrated in the sputum. The source of infection was in all probability tuberculous cows belonging to the farm at which the patient had been employed as milkmaid.

*Case 57.* Female, aged 42. Wife of a tenant-farmer, Rydsgård.

The father died of pulmonary tuberculosis in 1898, but the mother and the other children of the family are healthy. When 14 years old the patient was employed as a servant in a family where the mistress was affected with phthisis, and when 16 years of age in another family where the mistress afterwards died of pulmonary tuberculosis. At the age of 22 she was employed at a convalescent home for phthisical patients. She got married in 1914, and has given birth to 7 children. The husband and the children are healthy. During 1924—1927 the herd consisted of 12 cows, one of which was affected with tuberculosis. In later years the family has not possessed a permanent herd; recently there has been only one cow, which did not show any evidence of infectious tuberculosis. The patient has milked and also consumed raw milk.

During a short period in 1918 the patient had a *stitch in the right side of the chest*. She then felt well until some time after parturition in June 1929, when she began to *lose weight* and had a *cough* with yellowish green *sputum*. She began to have *night sweats* in July 1930, but the diagnosis of a right-sided exudative pulmonary tuberculosis was not made until the following month, August 1930. The radiographic examination revealed a cloudily mottled, partly confluent parenchymal opacity in the upper half of the right lung and a cavity about the size of a hazel-nut in I<sub>1</sub> on the same side. No evidence (calcifications, etc.) indicative of an earlier primary tuberculous infection could be observed within the regions of the lungs and hili (Fig. 27). Tubercle bacilli regularly occurred in the sputum. A right artificial pneumothorax was attempted in 1930—1932, but only a poor collapse of the lungs was obtained. After the lung had re-expanded, the cavity grew considerably, so that in August 1934 it was the size of a plum. Now changes were also observed for the first time in central part of the left lung (mottled condensation). The changes afterwards spread very slowly down into the lungs. With the exception of an artificial pneumothorax, the patient refused to submit to any form of surgical treatment. She died in April 1940. *Samples of the sputum* taken in March 1937 were found to contain abundant tubercle bacilli of the bovine type.

The *necropsy examination* (performed by Prof. E. SJÖVALL) gave the following result: The upper lobe of the right lung showed several cavities, up-



Fig. 27.

*Case 57.* A woman of 42 years (wife of a tenant-farmer) with *right-sided pulmonary tuberculosis*. The picture shows the appearance of the changes when the disease was diagnosed. In the upper half of the right lung there is a cloudy, mottled, partly confluent parenchymal density, and in  $I_2$  of the same lung is seen a less prominent, but indubitable, cavity the size of a hazel-nut. The changes progressed very slowly. Artificial pneumothorax did not change the condition; no other therapy was permitted. *Bovine tubercle bacilli* were abundantly present in the sputum. Death did not take place until 10 years after the diagnosing of the pulmonary affection.

to the size of plums, partly confluent, all of them being in free communication through the bronchial branches out towards the trachea. The walls of the cavities were thick, fibrous and indurated. The bronchial mucosa was thickened, hyperaemic, without any signs of tuberculous changes. In the right middle lobe there were several fresh acinous foci.

The right lower lobe was interspersed with fresh liquefactions, fairly equal in size, with grey, gelatinous margins. No caseous necrosis. At the apex of the left upper lobe there was an old specific change with fibrosis and a small central liquefaction. On pressure a greyish yellow pus escaped out of the bronchial lumina. The left lower lobe contained scattered acinous foci. The hilar glands were moderately enlarged and confluent, intensely anthracotic and caseated. No evidence of tuberculosis of the mesenteric nodes nor of tuberculosis of the intestines could be seen. Amyloid was met with in the spleen.

The *necropsy diagnosis* was: Tbc. chronica cavernosa et recent pulmonum + amyloidosis.

A 42-year-old woman with *right-sided pulmonary tuberculosis* (cavernous). Artificial pneumothorax treatment was ineffective. No other surgical therapy was allowed. The disease spread very slowly. Death did not take place until 10 years after the diagnosing of the pulmonary affection. Bovine T.B. were demonstrated in the sputum. The source of infection was not discovered.

*Case 58.* Female, aged 22. Unmarried, living at home. Father, farmer, Glimminge.

The parents and other children of the family in good health. The patient has assisted in the work on the farm, has also milked cows and consumed raw milk. It is not known whether tuberculosis has occurred among the cattle. The source of infection could not be traced.

In July 1937 the patient felt *fatigued*, had a *cough* and a *sore throat*. She had also a *stitch in the right side on a level with the shoulder-blade*. Radiographic examination of the lungs made in August of the same year revealed a large parenchymal opacity with central liquefaction at the right apex. The patient was not admitted to a sanatorium until October. In the meantime the changes had progressed considerably. In the right supra-clavicular region there appeared a compact density in the centre of which there was a walnut-sized cavity. Mottling could be seen medially to the density down towards the hilum (Fig. 28). *Bovine tubercle bacilli were abundantly present in the sputum*. The tuberculin reaction was positive and the rate of sedimentation 56 mm. The cervical lymph nodes were not tuberculous, nor were there any signs of a previous tuberculous infection (calcifications, etc.) within the areas of the lungs and hili. Right-sided pneumothorax treatment was instituted in October 1937 and was supplemented with cauterisation of adhesions in January 1938, which resulted in the closure of the cavity. Since then the patient's condition has gradually improved, but she is not yet able to work.

A woman of 22 with *exudative tuberculosis of the right lung* (cavernous). As the result of pneumothorax treatment, supplement-

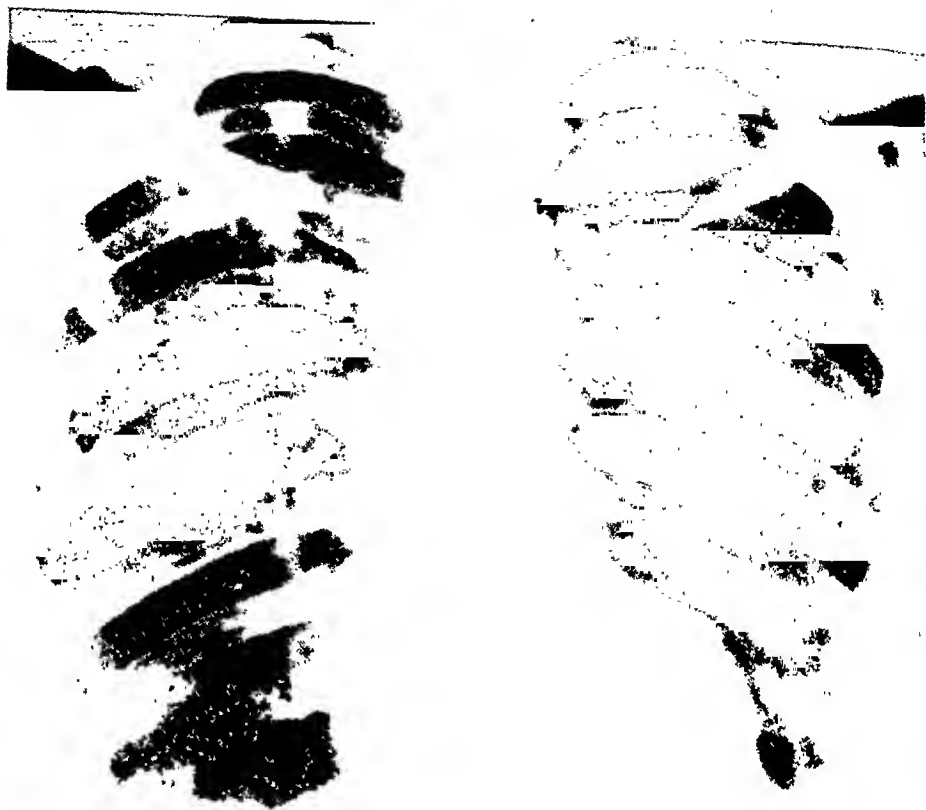


Fig. 28.

*Case 58.* An unmarried woman of 22 years, living at home (father, farmer) with *right-sided pulmonary tuberculosis*. The picture shows the appearance of the changes about two months after the diagnosis had been made. In the right supraclavicular region can be seen a compact density, in the centre of which is a walnut-sized cavity. Medially to the density a mottling can be seen right down to the hilum. *Bovine tubercle bacilli* were found abundantly in the sputum. During pneumothorax treatment, supplemented with cauterisation of adhesions, the changes have regressed. The patient's present health is good.

ed with cauterisation of adhesions, the condition has greatly improved and the changes reduced. Bovine T.B. occurred in the sputum. The present condition is good. The source of infection was not found.

*Case 59.* Female, aged 38. Wife of a farmer, Rynge.

The parents are healthy. A brother died of pulmonary tuberculosis in 1933, and a sister in 1937. The bacteria were not typed. The patient has



Fig. 29.

*Case 59.* A woman aged 38 years (wife of a farmer) with *left-sided pulmonary tuberculosis*. The picture shows the appearance of the changes two months after the diagnosis had been made. A density, the size of the palm of a man's hand, can be seen outside the upper part of the left hilar region and inside this density a cavity as large as a hazel-nut. *Bovine tubercle bacilli occurred sparingly in the expectoration*. Rapid progression in both lungs necessitated bilateral pneumothorax treatment, which nevertheless proved ineffective. *Death* took place about 17 months after the detection of the disease.

been married for 11 years. The husband has healed tuberculous lesions in the lungs. The children are in good health. The farm has 2 cows, which on veterinary examination in 1937 were found to be healthy. The animals had not been on the farm, however, for more than 2 years. No bovine tuberculosis is said to have occurred among them. The patient had milked and also consumed raw milk.

The patient was clinically examined (and radiographed) in 1928 and 1931, but no pulmonary changes could be discerned. In February 1937 she became acutely ill with a *high fever* and a *stitch in the left side of the chest*. Immediately outside the upper part of the left hilar region there could now be seen a compact density, as large as a hazel-nut, with rarefaction in the centre (a cavity). By April this density had grown to the size of the palm of a man's hand, while the cavity had increased to the size of a hazel-nut (Fig. 29). *Bovine tubercle bacilli were sparingly found*

in the sputum. The tuberculin reaction was positive and the sedimentation rate 62 mm. No tuberculosis of the cervical lymph nodes occurred, nor were any signs (calcifications, etc.) of an earlier tuberculosis discernible in the regions of the lungs and hili. The lesions progressed rapidly. In July they involved not only the whole of the left upper field but also the central parts of the right lung. Bilateral pneumothorax treatment was induced in July, but failed to stop the progress of the disease. A tuberculous empyema occurred on the left side. At about the same time symptoms also appeared of tuberculous tendovaginitis. The general condition deteriorated rapidly. Albumin had been regularly present in the urine since February. In April laryngeal tuberculosis appeared and the patient died in June 1938. There was no necropsy examination.

A woman of 38 with a *left-sided, exudative, pulmonary tuberculosis* (cavity). In spite of bilateral pneumothorax treatment the process spread rapidly to both lungs, to the tendon sheaths, to the larynx and possibly also to the kidneys. The patient died about 17 months after the diagnosis of the affection. Bovine T.B. were present in the sputum. The source of infection was not discovered.

*Case 60.* Female, aged 52. Wife of a farmer, Kyrkheddinge.

No tuberculosis in the family. The patient was born in Denmark but came to Sweden when only 2 years of age. Between 10—15 years of age she lived at Råby Children's Home, afterwards was employed as servant at different places until she got married in 1908. The family had a farm of its own for 12 years at Odarslöv. It is not known whether tuberculosis occurred among the cattle. The husband had pulmonary tuberculosis in 1927, which was found to have healed on a control examination made in 1930. Four years later he died from uraemia. In this marriage the patient had 8 children, all of whom are healthy. The patient was married a second time in 1936. The husband is in good health. The patient did the milking, and she also drank raw milk. The source of infection was not traced.

In 1909 the patient was laid up with a right-sided pleurisy for 3 months. In October 1936 she began to feel *tired* and *giddy*, had a *poor appetite* and *lost weight*. An examination made in this connexion revealed a right-sided, cavernous phthisis. The radiograms showed a considerable displacement of the heart and the mediastinum to the right, due to the previous right-sided pleurisy. Parenchymal changes of a tuberculous nature were found in the upper part of the right lung field, also a cavity as large as a mandarin (Fig. 30). The patient, however, refused to enter a hospital, and she could not be induced to do so until 10th February 1937. She had then been bedridden for some time on account of *cough*, *fever* and *night sweats*. The rate of sedimentation was 123 mm. The radiographic examination revealed that the changes had progressed considerably.



Fig. 30.

*Case 60.* A woman of 52 years (wife of a farmer) with *right-sided pulmonary tuberculosis* (27 years previously she had a right-sided exudative pleurisy). When the affection was diagnosed, the heart and the mediastinum were greatly displaced to the right owing to the previous pleurisy. In the upper part of the right lung field there was a cavity quite as large as a mandarin, surrounded by smaller tuberculous changes. *Bovine tubercle bacilli were sparingly found in the sputum.* The condition rapidly deteriorated. Death took place about 5 months after the affection had been diagnosed.

Thus a density the size of a man's hand had developed in the right I<sub>I</sub>—I<sub>III</sub>. The cavity had also increased in size. *Bovine tubercle bacilli were sparingly found in the sputum.* No tuberculosis of the cervical lymph nodes or any signs (calcifications, etc.) of an earlier tuberculous infection in the regions of the lungs and hili could be shown. The condition greatly deteriorated after a severe haemoptysis on 21st January. The patient died on 1st March 1937. Necropsy examination was not obtained.



A 52-year-old woman with *right-sided pulmonary tuberculosis* (cavernous) and considerable residues of an *exudative pleurisy* when 25 years old. She died about 5 months after the diagnosis of the pulmonary affection. Bovine T.B. were demonstrated in the sputum. The source of infection was not traced.

*Case 61.* Female, aged 20. Unmarried, living at home. Father, farmer, Löberöd.

The parents and other children in good health. Two first cousins died of pulmonary tuberculosis in 1927 and 1934 respectively. The patient was born and brought up in the country. She participated in the farm work but did not milk or tend cows. She had consumed raw milk. It is not known whether tuberculosis has occurred among the cattle. The source of infection was not discovered.

In March 1936 the patient manifested symptoms of *influenza*. She felt *tired* and *feverish*, had a *dry cough* and *headache*. An examination in May revealed a *right-sided pulmonary tuberculosis*. In the upper half of the right lung there was a mottled, partly confluent, parenchymal density and a cavity as large as a hen's egg in the right ScI—I<sub>1</sub> (Fig. 31). No evidence (calcifications, etc.) of a previous primary infection was discernible in the lung and hilar regions. Nor could any nodular calcifications be seen in the abdominal radiogram. The cervical lymph nodes were normal. *Bovine tubercle bacilli* were abundantly present in the sputum. A right artificial pneumothorax was induced in November 1936 and supplemented with cauterisation of adhesions in February 1937. In spite of this, closure of the cavity failed. The patient's condition gradually deteriorated, the tuberculous process relentlessly spread further into the lungs. Shortly afterwards signs of intestinal tuberculosis also appeared and the patient died later at her home. Necropsy examination was not obtained.

A woman of 20 with a *right-sided, pulmonary tuberculosis* (cavernous). In spite of pneumothorax treatment and cauterisation of adhesions the process spread rapidly. She died about 1 year and 9 months after the diagnosis of the disease. Bovine T.B. were present in the sputum. The source of infection was not traced.

*Case 62.* Female, aged 24. Wife of a farm-labourer, Bara.

The family history is free from tuberculosis. Since she was 15 years of age the patient had been employed as milkmaid at different farms. She had also consumed raw milk. It is not known whether tuberculosis occurred among the cattle. She was married in 1933, but still continued milking. She had milked as recently as 3 weeks before the disease was diagnosed. It is worthy of note that she was only a few months at her last

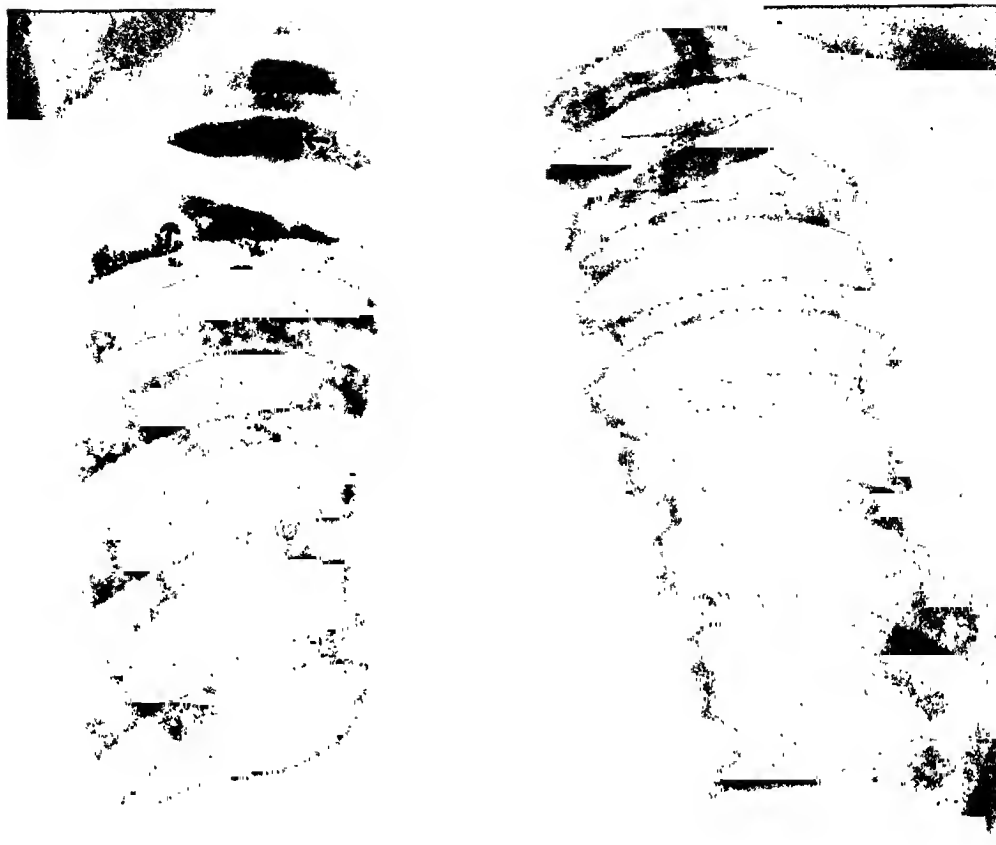


Fig. 31.

*Case 61.* A 20-year-old woman, living at home (father, farmer), with *right-sided pulmonary tuberculosis*. When the diagnosis was made, a mottled, partly confluent, parenchymal density could be seen in the upper half of the right lung, and in the right ScI-II there was a cavity nearly as large as a hen's egg. *Bovine tubercle bacilli were abundantly present in the sputum.* In spite of artificial pneumothorax, followed by cauterisation of adhesions, the changes progressed. *Death* took place about 1 year and 9 months after the diagnosing of the disease.

situation. Many of cattle on this farm, which had been non-reactors for a very long time, afterwards gave a positive tuberculin reaction. The only explanation of the tuberculous infection of the animals offered in the report of the investigation is that they had been infected by the milkmaid.

In May 1935 the patient had a *cold* and a *cough* for a couple of weeks. She was then well until the beginning of November, when the cough returned. She now felt *fatigued*, had *night sweats* and *lost weight*. At the end of December she began to complain of *dyspnoea* and a *stitch in the right side of the chest*. She was then also *hoarse* and had frequent attacks

of vomiting. The diagnosis of bilateral pulmonary tuberculosis was established in January 1936. In the lower two-thirds of the right lung field there was a mottled, greatly confluent parenchymal density, while in the upper one-third a cavity as large as a mandarin could be seen. Extensive tuberculosis changes in the form of spots, here and there confluent, were also observed in the lower two-thirds of the left lung. Moreover, large numbers of calcified nodes were discernible in both axillae and in the soft parts of the neck (Fig. 32), on the other hand, there were no signs (calcifications, etc.) of an earlier primary infection within the regions of the lungs and hili. *Bovine tubercle bacilli were very abundantly present in the sputum.* The rate of sedimentation was 79 mm. Small tuberculous changes were observable in the larynx. During the subsequent period of care the patient's condition rapidly deteriorated and she died in September 1936. Necropsy examination was not obtained.

A 24-year-old woman with *bilateral, exudative, pulmonary tuberculosis* (cavernous) and *tuberculosis of the larynx*, as well as *signs of a previous tuberculosis of the cervical and axillary lymph nodes*. She died about 9 months after the pulmonary affection had been diagnosed. Bovine T.B. were present in the sputum. The source of infection was not traced. *She almost certainly infected the herd on a farm where she had milked as recently as 3 weeks before the detection of the severe and extremely infectious lung lesions.*

*Case 63. Female, aged 21. Dressmaker, Father, farmer, Skurup.*

The paternal grandmother died of pulmonary tuberculosis in 1891. The father shows roentgenological evidence of a healed tuberculous primary complex, while the mother has only a few calcified spots in one lung. In other respects the family is free from tuberculosis. The patient was born and brought up in the country. At an early age she worked on the farm, milked cows, and she had also consumed raw milk. Lately she had been employed as a dressmaker. The herd consists of 4 cows. No tuberculosis is said to have occurred among the animals. The source of infection was not discovered.

In February 1935 the patient began to complain of a cough, she lost weight, frequently had night sweats and felt increasingly fatigued. But she continued working until June 1935, when it was found that she had a left-sided pulmonary tuberculosis. The whole of the left lung field was taken up by a mottled, here and there confluent, parenchymal density. On the other hand no evidence (calcifications, etc.) of a previous primary infection was discernible in the lung and hilar regions. On admission to a sanatorium in July the same year the changes had progressed. Thus, a cavity nearly as large as a hen's egg had developed at the apex of the left lung (Fig.

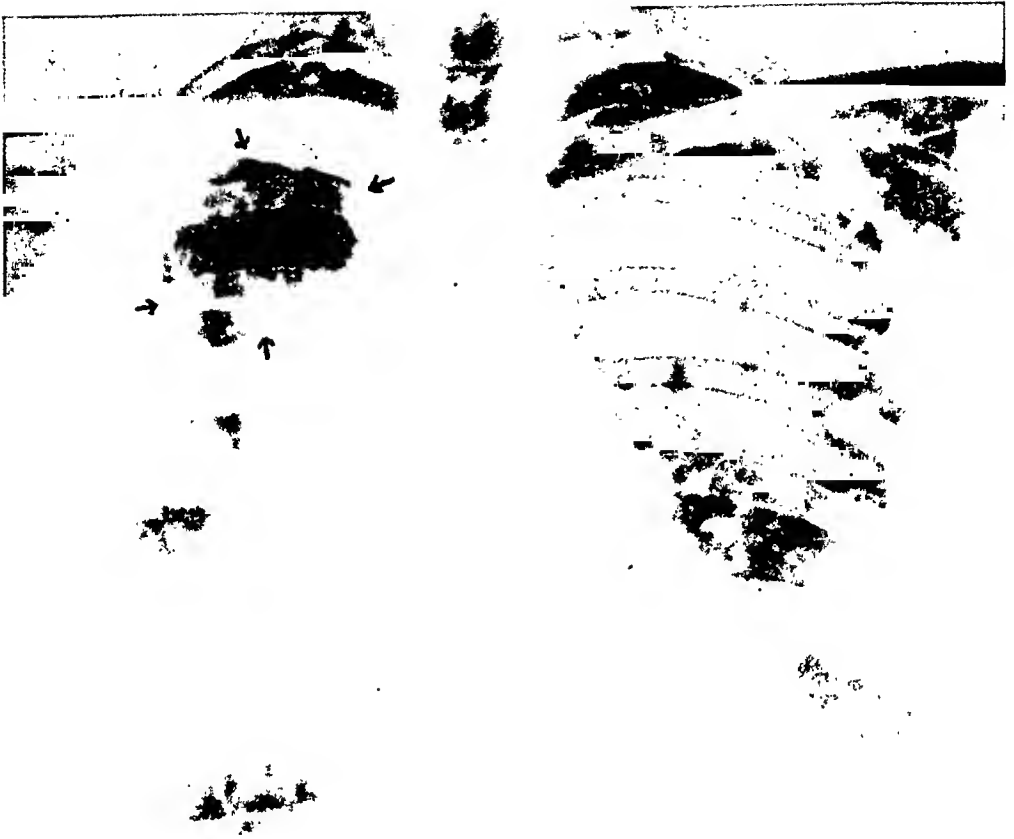


Fig. 32.

*Case 62. A woman of 24 years (wife of a farm-labourer) with tuberculosis of the larynx and bilateral pulmonary tuberculosis, in addition to evidence of a previous tuberculosis of the cervical and axillary lymph nodes. The picture shows the presence of a spotty, highly confluent, parenchymal density in the lower two-thirds of the right lung and a cavity as large as a mandarin in the upper one-third. Extensive, spotty, parenchymal changes are also visible in the left lung. Calcified lymph nodes can be observed in the axillae and the neck. Bovine tubercle bacilli occurred very abundantly in the sputum. The changes progressed rapidly, leading to death about 9 months after the diagnosing of the pulmonary affection.*

*The patient almost certainly infected the previously non-reactive herd on a large farm where she had milked only 3 weeks before the detection of the disease.*

33). The tuberculin reaction was positive. No tuberculosis of the cervical lymph nodes occurred. *Bovine tubercle bacilli* were found abundantly in the sputum. A left artificial pneumothorax was induced at once, but the cavity could not be made to close, in spite of a cauterisation of adhesions made shortly afterwards. Instead of closing the cavity became increasingly larger, so that a rupture into the pleura was feared. Changes soon appeared also in the right lung. A left phrenic evulsion was performed in February 1936. By this time tuberculous changes could also be shown in the right kidney, which was removed in March 1936. The kidney was found to be considerably enlarged, entirely interspersed with cavities, up to the size of a pigeon's egg, which were filled with caseous matter. Grave changes were also present in the right ureter, with ulcerations along its entire length. The condition had deteriorated by January 1937, extensive tuberculous changes being found in both lungs. The patient died in March 1937. There was no necropsy examination.

A 21-year-old woman with *left-sided, exudative pulmonary tuberculosis* (cavernous). Despite a left artificial pneumothorax, followed by cauterisation of adhesions, and afterwards phrenic evulsion the cavity could not be closed nor the spread of the process arrested. The tuberculous changes progressed rapidly in both lungs. *Right-sided renal tuberculosis* also developed. The patient died about 1 year and 10 months after the disclosure of the pulmonary affection. Bovine T.B. were demonstrated in the sputum. The source of infection was not traced.

*Case 64.* Male, aged 25. Farm-labourer, Lyby.

The parents and other children healthy. The patient lived at home until he was 22 years of age, when he attended the People's High School at Ljungskile for 7 months. After leaving this school he again lived at home. He was not very interested in farming or tending cattle, therefore, he very seldom visited the cow-stalls. He drank milk very reluctantly. For the last 25 years the herd on the farm has consisted of about 20 cattle, 16 being milch cows. As far as is known, no tuberculosis of the udder has occurred, nor has tuberculosis been detected on slaughter. Neither did the clinical examination of the herd furnish any grounds for assuming that the patient had been infected at home. Infection probably occurred during the period he was away from home. The source of infection could not be traced.

Diabetes mellitus was diagnosed in 1936. In February 1937 he complained of a «cold», and a *persistent cough* and *fever* appeared. Left-sided pulmonary tuberculosis was diagnosed a month later. In the middle one-third of the left lung there appeared a confluent, cloudy mottling and a walnut-sized cavity laterally in I<sub>II</sub> (Fig. 34). No evidence of a previous



Fig. 33.

*Case 63.* A dressmaker aged 21 years (father, farmer) with *left-sided pulmonary tuberculosis*. When the diagnosis was made the whole of the left lung field showed a spotty, here and there confluent, parenchymal density. After a short time a cavity as large as a hen's egg appeared at the apex of the left lung. *Abundant bovine tubercle bacilli were found in the sputum.* In spite of artificial pneumothorax, later supplemented with cauterisation of adhesions and phrenic evulsion, the disease continued to spread. *Death* occurred about 1 year and 10 months after the detection of the affection.

primary tuberculous infection (calcifications, etc.) could be seen in the lung and hilar regions, nor did the abdominal radiogram reveal any signs of calcified lymph nodes. The cervical lymph nodes were normal. The

tuberculin reaction was positive and the rate of sedimentation 23 mm. *Bovine tubercle bacilli* were found very abundantly in the sputum. A left artificial pneumothorax was induced on 25th March. Although a very satisfactory collapse of the lung was obtained, the cavity continued to increase, so that in May it was as large as a plum. The condition afterwards gradually grew worse. In October spontaneous pneumothorax occurred on the right side and the patient died on 2nd December 1937. There was no necropsy examination.

A 25-year-old man with *left-sided, exudative pulmonary tuberculosis* (cavernous). In spite of a left artificial pneumothorax and a satisfactory collapse of the lung, the cavity could not be obliterated, but continued to grow larger. Later the process spread to the right lung, causing a spontaneous pneumothorax on that side. He died about 10 months after the affection had been diagnosed. *Bovine T.B.* were cultivated on two different occasions from the sputum. The source of infection was not discovered.

*Case 65.* Female, aged 31. Wife of a farm-labourer, Löberöd.

The father died as the result of an accident. The mother, the husband and 3 children are healthy. One child has tuberculous lymphomata on the neck. The patient, who was born and brought up in the country, had been employed as milkmaid at different farms. She had also drunk raw milk. It is not known whether tuberculosis occurred among the cattle. The source of infection was not traced.

In May 1934 the patient had a *cough*, which was at first dry, but large quantities of *expectoration* were later coughed up. Shortly afterwards she became *hoarse* and had a *stitch* dorsally on the left side. After a confinement in June 1934 her condition deteriorated considerably. She now had a high *fever*. In July left-sided pulmonary tuberculosis was diagnosed. In the apex of the left lung there appeared a cavity nearly as large as a plum and just below it another cavity the size of a hazel-nut. In the surroundings, especially medially, a rather diffuse parenchymal density could be seen (Fig. 35). On the other hand, no signs of an earlier primary infection (calcifications, etc.) were discernible in the regions of the lungs and hili nor in the abdomen. *Bovine tubercle bacilli* were abundantly found in the sputum. The cervical lymph nodes were normal. The tuberculin reaction was positive. A left artificial pneumothorax was induced almost at once, and owing to the spread of the process to the right lung in September 1934 pneumothorax treatment became necessary on that side too. The cavities in the left lung at first closed well but they soon began to increase again, in spite of the fact that the lung had collapsed satisfactorily. In July 1936 tuberculosis of the larynx was detected. Oleothorax treatment of the left lung did not result in the closure of the



Fig. 31.

*Case 64.* A 25-year-old farm-labourer with *left-sided pulmonary tuberculosis*. The condition at the time the affection was diagnosed is shown in the picture. In the middle field of the left lung there occurred a confluent, cloudy mottling and laterally in III there was a walnut-sized cavity. *Bovine tubercle bacilli* occurred very abundantly in the sputum. The changes progressed in spite of pneumothorax treatment. Death took place about 10 months after the diagnosing of the affection.

cavities; the patient still continued to be highly infectious. She died in September 1937 after repeated haemoptyses. There was no necropsy examination.

A woman of 31 with *left-sided pulmonary tuberculosis* (cavernous). In spite of artificial pneumothorax, followed later by oleothorax treatment, the cavities could not be made to collapse.



The process spread irresistably; *tuberculosis of the larynx* appeared. The patient died about 3 years after the diagnosis of the disease. Bovine T.B. were present in the sputum. The source of infection was not discovered.

*Case 66.* Female, aged 19. Wife of a farm-labourer, Börringe.

The parents are in good health. A maternal aunt had pulmonary tuberculosis in 1935, but the patient had not met her for 8 years. The husband is healthy. The only child was admitted to hospital in 1936 (at the age of 3 months) under the diagnosis of tuberculous infection + rickets + spasmophilia + anaemia. The tuberculin reaction was positive. The radiological examination of the lungs showed nothing abnormal. Since the age of 13 the patient had been employed as a servant at different farms. She took part in milking; and had also consumed raw milk. It is not known whether tuberculosis occurred among the cattle. The herd belonging to the farm at which she was last employed was non-reactive to tuberculin. The source of infection was not traced.

In November 1935 the patient had a *nasal catarrh*, *sore throat* and *expectorated* a moderate quantity of *greenish sputum*. She soon afterwards had *fatigue*, *loss of appetite* and a *stitch in the right side of the chest*. Bilateral pulmonary tuberculosis was diagnosed in February 1936. Extensive spotty parenchymal densities were present in both lungs, two large cavities being also seen at the base of the right lung. On the other hand, no evidence (calcifications, etc.) of a previous tuberculous primary infection was discernible in the lung and hilar regions (Fig. 36). The radiographic examination of the abdomen revealed no calcified lymph nodes. The cervical lymph nodes were normal. The tuberculin reaction was positive and the rate of sedimentation 126 mm. *Bovine tubercle bacilli* were very abundantly present in the sputum. Bilateral pneumothorax was induced in August 1936, followed later by right-sided cauterisation of adhesions. But closure of the cavities was not obtained and the patient's condition deteriorated. Symptoms of intestinal tuberculosis appeared. The patient died on 4th February 1937. There was no necropsy.

A 19-year-old woman with a very advanced *bilateral pulmonary tuberculosis* (cavernous). In spite of bilateral artificial pneumothorax and right-sided cauterisation of adhesions the closure of the cavities was not obtained. *Intestinal tuberculosis* developed. The patient died about 1 year after the disease had been diagnosed. Bovine T.B. were present in the sputum. The source of infection was not discovered.

*Case 67.* Male, aged 68. Farmer, Svedala.

No family history of tuberculosis. The patient, who previously had a



Fig. 35.

*Case 65. A woman of 31 years (wife of a farm labourer) with left-sided pulmonary tuberculosis. The picture shows the appearance of the changes at the time the affection was diagnosed. At the apex of the left lung there was a plum-sized cavity, below which there was another cavity the size of a hazel-nut. A compact density is seen medially to the cavities. Abundant bovine tubercle bacilli were found in the sputum. In spite of artificial pneumothorax, followed later by oleothorax treatment, the process continued to spread. The patient died about 3 years after the disease had been diagnosed.*

small farm, had milked and also consumed raw milk. No information is available as to whether tuberculosis occurred among the cattle.

The patient had had a *cough* for about a year or two. In March 1936 the cough increased and he now had *sputum* and felt *fatigued*. Afterwards his strength rapidly declined. *Fever* developed. He lost about 10 kilos in a year. He was admitted to hospital on 30th September 1936, where he died of pulmonary tuberculosis already on 12th October. Both lungs were interspersed with spotty parenchymal densities. At the apex of the left lung there was a plum-sized cavity (Fig. 37). The radiographic examination



Fig. 36.

*Case 66.* A woman aged 19 years (wife of a farm-labourer) with *bilateral pulmonary tuberculosis*. When the diagnosis was made (see above) extensive, spotty parenchymal changes could be seen in both lungs. At the base of the right lung there were also two large cavities. *Bovine tubercle bacilli* were found very abundantly in the sputum. Despite bilateral pneumothorax treatment, supplemented with cauterisation of adhesions on the right side, the patient died about 1 year after the detection of the disease.

revealed no signs (calcifications, etc.) of a previous primary infection in the regions of the lungs and hili. The sedimentation rate was 54 mm. *Bovine tubercle bacilli* were abundantly present in the sputum.

The report of the necropsy (performed by Dr. F. Koch) was: Section through the different lung lobes everywhere showed the presence of an acino-nodose tuberculosis. The cavity in the left upper lobe had a well-defined wall. Like the cavity, the drainage bronchus was abundantly filled with masses of mucopurulent matter. In the larynx there were several typical tuberculous ulcerations, which were also met with in the small intestine. The mesentery contained partly old, calcified nodes, partly fresher, slightly haemorrhagic, swollen lymph nodes.



Fig. 37.

*Case 67. A farmer aged 68 years with bilateral pulmonary tuberculosis. When the disease was diagnosed the lungs were covered with spotty parenchymal densities. In addition there was a plum-sized cavity in the left apical field. Abundant bovine tubercle bacilli were present in the sputum. The condition deteriorated very rapidly. Death took place already after 2 weeks.*

*The necropsy diagnosis was: Tbc. pulm. amb. c. cavern. lob. sup. pulm. sin. + tbc. intestini + tbc. laryngis.*

A 68-year-old man with *bilateral pulmonary tuberculosis* (cavernous), which resulted in his death only 2 weeks after the affection had been diagnosed. Bovine T.B. were demonstrated in the sputum and in the mesenterial lymph nodes. The source of infection was not traced. The necropsy examination revealed the presence of an *old tuberculosis of the abdominal lymph nodes*.

## B. Analysis of the Material.

As already mentioned, 67 cases of bovine tuberculosis in man were detected in typings of tubercle bacilli during the years 1936—1939 in the southernmost part of Sweden (the Province of Skåne). An additional 27 cases have been diagnosed while the work was being collocated. As these latter cases agree completely as regards behaviour, appearance and course with those previously observed they have not been included in the present series, but will be mentioned occasionally in the classification. Of these new cases 1 had no demonstrable tuberculous changes, although bovine tubercle bacilli were found in the stomach washing, 3 showed the picture of a primary complex with pulmonary and hilar changes. The others had tuberculous meningitis (1 case), tuberculous pleurisy (2 cases), tuberculous peritonitis (1 case), tuberculosis of the cervical lymph nodes (5 cases), bone tuberculosis (4 cases), urogenital tuberculosis (2 cases) and pulmonary tuberculosis (8 cases).

*Thus altogether 94 cases of bovine tuberculosis in man have been discovered in Skåne.* A detailed report (v. Case Histories, p. 19) has already been given of 67 of these cases. The number of cases found, however, certainly constitutes only a small part of the actual cases of bovine tuberculosis in man occurring in Skåne. The reason for this is that the main object of the investigation was to ascertain the number of *pulmonary* tuberculosis cases in Skåne due to the bovine type of bacillus. The investigation is therefore as complete as possible only in so far as pulmonary tuberculosis is concerned, a form of the disease, according to all experience, that is less frequently due to the bovine bacillus than other tuberculous manifestations, such as tuberculosis of bones and lymph nodes, meningitis, peritonitis, urogenital tuberculosis, etc. Material from the latter were also examined, it is true, but only to a small extent. Nor was any pressure exercised so as to get a more general sending in of such material for examination. Further support to the above assertion that the number of cases of bovine tuberculosis in Skåne is much higher than that indicated by the figures recorded above is afforded by the fact that the present series consists of only a small number of children (Tables 2—3), in whom bovine tuberculosis

is especially common, owing to the large quantities of cow's milk ingested. The number of cases observed is nevertheless sufficient to convey a rather good idea of the clinical picture of bovine tuberculosis in man.

The present material thus consists of 67 cases. A great many radiograms illustrate the appearance of the tuberculous changes at the time the disease was diagnosed. For the sake of surveyability, the essential data of the case histories have been summarized in two large tables, one of which (Table 5) gives the more important anamnestic information, the occurrence and development of the changes. The other table (Table 7) furnishes particulars of the symptomatology of the cases of bovine tuberculosis and the appearance of the changes when the disease was diagnosed.

From Table 2 it will be seen that 33 of the 67 cases were males and 34 females. *Thus in the present material there is no sex difference in the distribution of the tuberculous cases.* The same result will be obtained if the cases are divided into groups according to the localisation and appearance of the changes (Table 6). Only in the group of pulm. tbc. (Group 10) is the frequency among the females higher than among the males. Of the 28 cases belonging to this group 11 were males and 17 females (Table 8, page 149). The number of cases, however, is too small to permit any definite conclusion being drawn from this difference. Still the distribution between the sexes agrees with that in *pulmonary tuberculosis* due to the *human* type of bacillus, which form of the disease is undoubtedly more frequent among females than among males in Skåne.

Table 2 shows also *the ages of the patients at the time the disease was diagnosed.* The figures show, that the cases of bovine tuberculosis are distributed remarkably evenly among the different age groups from < 1 year up to 42 years, afterwards decreasing in frequency. In three cases bovine pulmonary tuberculosis was first detected at such an advanced age as 62—68 years, which must be considered to be very surprising. Finally, if the material is classified into 3 age groups, 0—4 years, 5—14 years and > 15 years, as done by some authors, the result will be that shown in Table 3. The figures in brackets (Table 3) denote the new cases of bovine tuberculosis detected after the conclusion of the investigation. As

Table 2.  
*Age at the time of diagnosis.*

Age	M	F	Total	Age	M	F	Total
<1 year	1	1	2	24 years	0	2	2
1 "	2	1	3	25 "	3	1	4
3 years	1	0	1	26 "	0	1	1
4 "	0	2	2	28 "	0	2	2
5 "	2	1	3	29 "	2	1	3
6 "	2	0	2	30 "	0	2	2
7 "	2	1	3	31 "	0	1	1
10 "	0	1	1	32 "	1	0	1
12 "	0	1	1	34 "	1	1	2
14 "	1	0	1	35 "	0	1	1
16 "	3	0	3	38 "	0	1	1
17 "	1	1	2	40 "	2	0	2
18 "	1	2	3	41 "	1	0	1
19 "	0	1	1	42 "	0	1	1
20 "	1	1	2	47 "	1	0	1
21 "	1	2	3	52 "	0	1	1
22 "	0	1	1	62 "	0	1	1
23 "	2	2	4	68 "	2	0	2
	20	18	38	Total	33	34	67

Table 3.

Age	Males	Females	Total
0-4 years	4 (5)	4 (1)	8 (6)
5-14 "	7 (4)	4 (2)	11 (6)
>15 "	22 (11)	26 (4)	48 (15)
Total	33 (20)	34 (7)	67 (27)

appears from the table, the material contains only a few children, a fact already mentioned. The majority of the patients belong to the  $> 15$  years age group. It would be of great interest to learn in what age groups the patients were when the different tuberculous manifestations were demonstrable. A critical examination of the

cases from this point of view shows that miliary tuberculosis, meningitis and peritonitis occurred exclusively among the children. Primary pulmonary lesions, tuberculosis of the lymphatic nodes and bone tuberculosis were in this material somewhat more common or about as common among the children as among the adults. On the other hand, nearly all cases of pulmonary tuberculosis, pleurisy and urogenital tuberculosis occurred among the adults. The material is of course too small to warrant any definite conclusion being drawn from this. *It nevertheless appears as if the different changes in bovine tuberculosis occur at about the same period of life as those following infections by the human tubercle bacilli.*

Table 4.

Occupation	Males	Females	Children	Total
Veterinarians, butchers, farmers, tenant-farmers, cowmen, farm-servants, farm-labourers (their wives or children) .....	14	14	15	43
Other occupations .....	8	12	4	24
Total	22	26	19	67

The *occupations* of the different tuberculous cases are shown in Table 4. Some authors have asserted that *bovine tuberculosis is an occupation disease*, especially affecting those people living in more regular contact with cattle. In order to ascertain whether that is the case even in my material, I have divided the occupations of the patients into two large groups, according to the more or less intimate contact of those engaged in these occupations with cattle. The first group consists of veterinarians, butchers, farmers, tenant-farmers, cowmen, farm-servants, farm-labourers, their wives or children. The second group comprises persons engaged in occupations other than those mentioned in the first group. This second group includes plumbers, metal-workers, building-trade operatives, textile workers, stone-cutters, brickyard workers, transport-workers, labourers, taxi-drivers, painters, shop-assistants, domestic servants, etc. and the wives or children of such persons. The table



shows very clearly the great risk run by those persons engaged in the occupations included in the first group. Not less than 43 of the 67 cases of bovine tuberculosis occurred among persons belonging to this group.

*But even if no regard is paid to the occupational risk itself, there cannot be any doubt that the risks of acquiring a bovine tuberculous infection are very much greater in rural districts than in towns.* At the end of 1938 the population of Skåne amounted to 773,363 persons, 447,025 living in the rural districts and 326,338 in towns. In spite of the high figure for the urban population it is represented in this material by only 14 cases, and several of these cases almost certainly acquired their bovine infection during an earlier stay in the country (Cases 23, 30, etc.). The other 53 cases were found in the rural districts. The reason why the risk of infection is greater among the rural population is rather obvious. In towns pasteurised milk or so-called Certified Milk, i.e. milk from tuberculosis-free herds, which are under continuous control, is drunk almost exclusively. On the other hand, in the country, where the workmen's wages often include milk for household consumption, raw milk is drunk to a very great extent. That was so, for instance, in not less than 56 of the 67 cases. Moreover, the rural population—in contrast to the urban population—is exposed to the risk of a direct transmission of tubercle bacilli from cattle (by dirt, inhalation), especially when tending or milking the animals. 29 of the 67 patients had milked cows. That a direct transmission of the infection took place in some of these cases will be shown below.

In spite of an investigation carried out for that purpose, *the source of infection* was discovered in only 15 of the 67 cases. The reason for this is that the changes were as a rule not entirely fresh when first detected. Further, in some cases the patients had changed situations several times in recent years. In the cases affected with tuberculosis of the cervical lymph nodes, bone, urogenital and pulmonary tuberculosis, there was probably, as a rule, a relatively long interval between the primary infection and the appearance of the morbid changes (Groups 7—10, Table 6), for the source of infection was discovered in only 3 of the 50 cases belonging to these groups. But it was quite a different matter when the tuberculous infection was fairly fresh. Thus, for instance, the source of infection

could be shown in 8 of the 9 cases affected with hilar or pulmonary changes (or both) occurring in association with or shortly after the primary infection (Group 2, Table 6). If we include the cases of miliary tuberculosis, tuberculous meningitis, tuberculous pleurisy, tuberculous peritonitis, etc. (Groups 1—6), the source of infection was found in not less than 12 of the 17 cases.

Since the source of infection was not always discovered and some of the patients had moved from one place of work to another, a map showing where the patients lived when their affection was diagnosed would be of only a limited value. Owing to the fact that the patients nearly always moved within the borders of the same county, it is nevertheless possible to obtain some idea, although somewhat uncertain, of the distribution of the tuberculous cases within the two counties which together form the Province of Skåne, viz. the counties of Malmöhus and Kristianstad.

Fig. 38 shows all the described cases of bovine tuberculosis, while Fig. 39 records only the cases of bovine primary, secondary and tertiary *pulmonary* tuberculosis in man (Cases 2—12, 15, 19, 29, 39—67). The maps represent the southernmost part of Sweden, the Province of Skåne. The boundary-line between the two counties of Malmöhus and Kristianstad is marked by a jagged line running downwards from left to right. The pin-heads mark the locations of the bovine cases when the disease was diagnosed. From the maps it will be seen that nearly all cases of bovine tuberculosis were found in the county of Malmöhus. It is especially noteworthy that all cases of bovine *pulmonary* tuberculosis occurred in that county, as this category of cases was investigated very carefully. Tuberculosis in cattle is exceedingly common also in the county of Kristianstad, therefore a more uniform distribution of the cases of bovine pulmonary tuberculosis in man might have been expected in the Province of Skåne. The cause why the bovine cases in man were nevertheless most common in the County of Malmöhus will be discussed later by *Lindau* and *Magnusson* in their papers.

In 32 of the 67 cases other members of the family had previously had or still manifested evidence of tuberculosis, which was *undoubtedly* of bovine origin in some cases. Thus Cases 2—4, two sisters and a brother, became ill at the same time as three more children of the family. The latter had about the same general symptoms

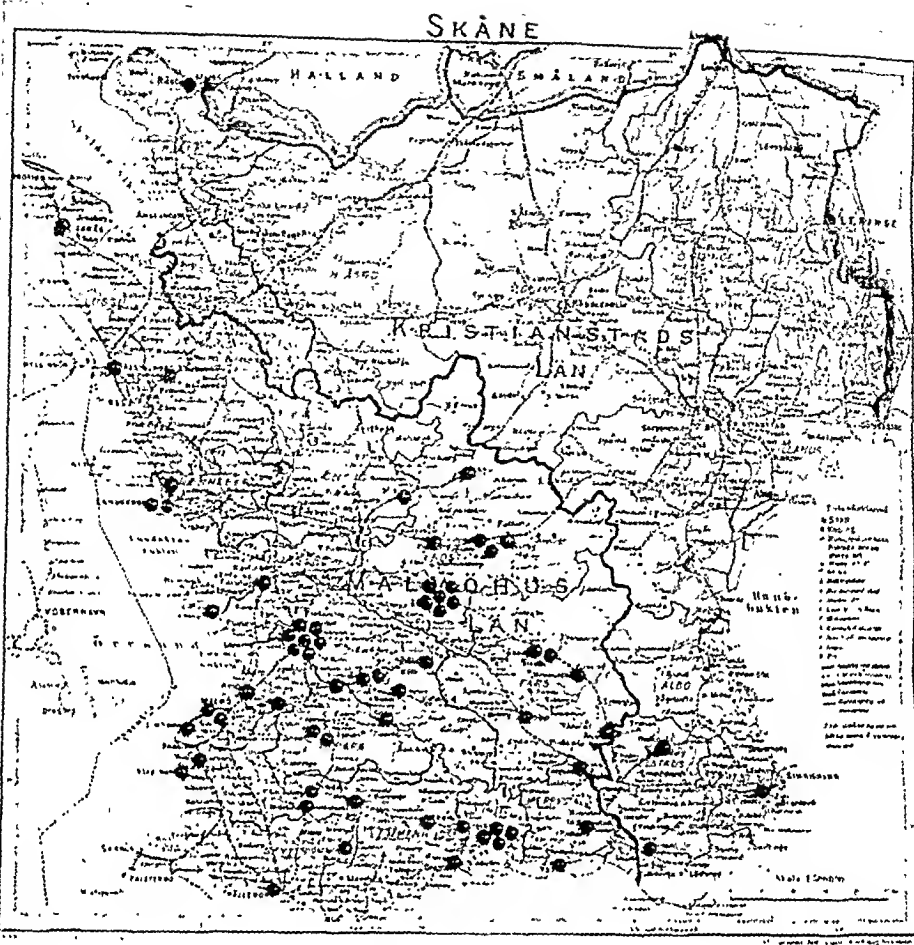


Fig. 38. Cases of bovine tuberculosis in man in the Province of Skåne.

as the former and were so ill that they required several months' institutional care. One of them had also erythema nodosum and hilar adenitis. Although no tubercle bacilli could be demonstrated, thus excluding the cases from this classification, there can hardly be any doubt that they also had bovine tuberculosis. The source of infection was tuberculous cattle on the farm. About the same thing applies to Case 5, who fell ill at the same time as 3 more children of the family. One of the latter had erythema nodosum, another had erythema nodosum and a primary complex in the right lung and hilar region, while the third developed intestinal tuberculosis. As examinations failed to reveal tubercle bacilli, these

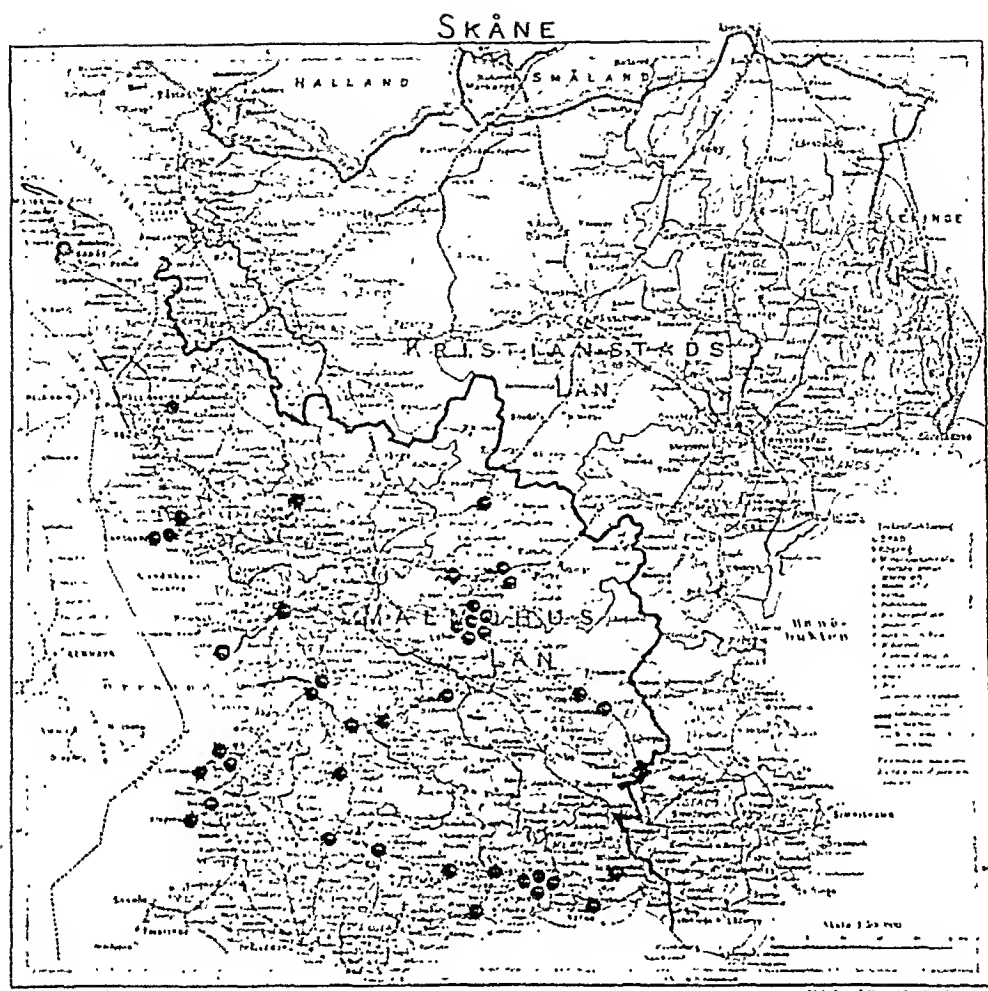


Fig. 39. Cases of *bovine* primary, secondary and tertiary *pulmonary tuberculosis* in man in the Province of Skåne.

children have not been included in the present series, although there can hardly be any doubt as to the etiology of the disease. In these cases, too, the source of infection was tuberculous cows on the farm.

Bovine tuberculosis certainly occurred also in a half-brother of Case 17, both of whom had drunk raw milk from a herd, among which not less than 13 animals were found to be affected with open tuberculosis. As the result of this severe infection the patient developed the lymphogland. region. coll. et bronchial. Bovine tubercle bacilli were present in the gastric lavage. This case was not observed

until after the conclusion of the investigation and, for reasons already mentioned, is not included in the classification. Cases 8 and 49 are two sisters with bovine tuberculosis. These two cases are of exceedingly great interest, as they may have transmitted the infection to one another. But before *bovine tuberculosis can safely be said to be transmitted by inhalation from one human being to another* the following conditions must be fulfilled. Phthisis should not be present in both cases, for in that event they may have been infected at the same time — perhaps long ago — by milk from tuberculous cows. Further one of them should have a cavernous phthisis with abundant tubercle bacilli in the sputum, and the other should have acquired a primary complex in the lung and hilar regions or a hilar adenitis. *Bovine* tubercle bacilli must be demonstrated in both of them. Finally, the possibility of a fresh infection from cattle must be excluded. It goes without saying that it is extremely seldom that all these conditions can be fulfilled, but Cases 8 and 49 (Figs. 6, 7, 19) do so.

Tuberculous changes of *probably* bovine etiology were found in the mother and two sisters of Case 18. On a radiological examination of the abdomen the mother showed a packet, nearly as large as a goose's egg, of hazel-nut-sized calcified lymph nodes in the median line on a level with  $L_I$  and  $L_{II}$ , and also calcareous spots the size of grains of rice in the upper part of the abdomen, which may represent calcifications in the liver, the spleen and the peritoneum. A sister had a bean-sized collection of calcified mesenteric nodes, and another sister had a calcified patch as large as a broad-bean above the central part of the sacrum. In these cases the suspicion of bovine etiology is based of course on the extensive calcifications in the abdomen and the simultaneous absence of any demonstrable tuberculous changes elsewhere. It is also worthy of note that three more children in this family had an increased rate of sedimentation for a long time, but no tuberculous changes could be detected.

Thus in a number of cases changes of a more or less certain bovine origin were found in other members of the family. Two cases (Cases 42 and 45) had tuberculous relatives, but the typing of the bacilli revealed that the changes were due to the *human* tubercle bacillus. In the other cases the bacilli could not be typed, either because the patients in question had already died or were no longer infectious

when the investigation was started. In most cases it is therefore impossible at present to determine whether the tuberculous changes found in the relatives of the patients were of human or bovine origin. There is nothing, however, that goes to show that the etiology of the changes must necessarily be bovine. The markedly high frequency of tuberculous changes in the relatives of these cases of bovine tuberculosis only implies that these families may have had a reduced resistance to tuberculous infections on the whole.

From Table 5 it will also be seen that the bovine cases had rather frequently had *earlier diseases* of importance. Thus diabetes mellitus occurred in 3 cases (Cases 40, 48 and 64). Of greater interest, however, is the presence of earlier tuberculous changes or residues of such lesions, as by that means it may be possible to determine with some degree of certitude the location of the primary infection, in other words, the route of infection. Among diseases preceding the present changes may be mentioned erythema nodosum alone (Cases 39 and 49) or erythema nodosum accompanied by a tuberculous primary complex in the lung, as well as pulmonary tuberculosis (Case 15), and, further, scrofula (Case 46) and exudative pleurisy (Cases 45, 48 and 60). Rests of earlier tuberculous lesions were found in several cases. Thus I found calcified residues of a primary complex in the lung (Cases 28 and 34), of a hilar adenitis (Cases 47 and 51), of tuberculosis of the cervical and axillary lymph nodes (Case 62), of tuberculosis of the abdominal lymph nodes (Cases 35, 36, 52, 53, 55 and 67). In two of the last-mentioned cases (Cases 52 and 53) tuberculosis of the cervical lymph nodes occurred at the same time. Finally, calcified rests of a pulmonary tuberculosis were noted in one case (Case 38). The route of infection, however, is also apparent from the location of the initial changes in a *fresh* bovine infection, and also from the result of the post-mortem examination. I shall recur later to this extremely interesting question, so important for the campaign against bovine tuberculosis.

In order to give the reader a more lucid survey, the bovine cases have been referred to one of the following groups (Table 6) according to *the nature and location of the changes*. The grouping is rather schematic, as several of the tuberculous cases had simultaneous changes in different parts of the body. In referring the cases

Table  
Survey of the Cases of

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
1	F	4	Father, farm-labourer	Country	Mother has stationary, non-bacillary pulmonary tuberculosis	Yes	No	No	—
2	F	5	Father, crofter	Country	Cases 2—4 are brothers and sisters. Maternal aunt and uncle died of pulmonary tuberculosis. The patients have never met them. Father had exudative pleurisy at 8 years of age. Three more children of the family became ill at the same time as the patients, but no bacilli could be shown. One of them had <i>erythema nodosum</i> and <i>hilar adenitis</i> .	Yes	No	Yes	—
3	M	7	Father, crofter	Country		Yes	No	Yes	—
4	F	10	Father, crofter	Country		Yes	No	Yes	—
5	M	16	Father, farm-labourer	Country	Three more children in the family were taken ill. No bacilli, however, could be shown. One of them had <i>erythema nodosum</i> , another <i>erythema nodosum</i> and a primary complex. The third had abdominal tuberculosis.	Yes	No	Yes	—
6	M	29	Farmer	Country	—	Yes	Yes	No	—
7	M	14	Father, farmer	Country	—	Yes	Yes	Yes	—

5.

*Bovine Tuberculosis.*

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bovine T.B. infection (no demonstrable tuberculous manifestations)	Stomach washing	Observation	No tuberculous changes have since appeared	Good	—
Erythema nodosum, hilar adenitis and pulmonary tuberculosis with atelectasis (primary complex) (Fig. 1)	Sputum, stomach washing	Hospital care	Regression	Good	—
Erythema nodosum and hilar adenitis (Fig. 2)	Stomach washing	Hospital care	Regression	Good	—
Erythema nodosum and hilar adenitis	Sputum, stomach washing	Hospital care	Central tuberculous changes in the left lung 1 year later. Afterwards a slow regression of the changes	Good	—
Erythema nodosum, hilar adenitis and pulm. tbc. (primary complex)	Stomach washing	Hospital care	Regression	Good	—
Hilar adenitis and pulm. tbc. (primary complex) (Fig. 3)	Sputum, stomach washing	Hospital care	Regression	Good	—
Hilar adenitis and pulm. tbc. with atelectasis (primary complex) (Figs. 4—5)	Sputum, stomach washing and tuberculoma	Hospital care	The changes slowly regressed. Later a tuberculoma appeared in the cerebellum. Died about 1 year after onset of disease.	Dead	—



Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest.
8	F	7	Father, farmer	Country	A sister had cavernous phthisis of bovine origin (Case 49)	Yes	No	Yes	—
9	M	23	Student at Vet. Coll.	Town	—	?	No	Yes	—
10	F	30	Living at home. Father, crofter.	Country	—	Yes	Yes	Yes	—
11	M	6	Father, church-caretaker	Country	Paternal uncle has formerly had pulm. tbc.; now non-bacillary and well	Yes	No	No	—
12	M	15 mths	Father, groom	Country	—	Yes	No	Yes	—
13	F	7 mths	Father, farmer	Country	Maternal aunt died of pulm. tbc. long ago	Yes	No	No	—
14	F	23	Living at home. Father, farmer	Country	—	No	Yes	Yes	—
15	M	41	Parish constable	Country	—	Yes	No	No	Erythema nodosum, tuberculous primary complex in the lung and incipient pulm. tbc. in 1934
16	M	16 mths	Father, farm-labourer	Country	—	Yes	No	Yes	—

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Erythema nodosum, hilar adenitis and pulm. tbc. (primary complex) (Figs. 6—7)	Stomach washing	Hospital care	Regression	Good	—
Erythema nodosum, hilar adenitis and pulm. tbc. (primary complex)	Sputum	Hospital care	Regression	Good	—
Hilar adenitis, pulm. tbc., tbc. of mediastinal lymph nodes (primary complex) (Figs. 8—9)	Pleural exudate, lung tissue	Hospital care. Artificial pneumothorax	The lung changes progressed. Later military dissemination to various organs. Died about 13 months after diagnosis of tbc	Dead	Yes
Bovine primary tbc. in the abdomen, acute military tbc. and tbc. meningitis (Fig. 10)	Cerebrospinal fluid	Hospital care	Died about 1 month after detection of tbc.	Dead	Yes
Bovine primary tbc. in the abdomen, acute military tbc. and tbc. meningitis	Cerebrospinal fluid	Hospital care	Died 8 days after detection of tbc.	Dead	Yes
Tuberculous meningitis	Cerebrospinal fluid	Hospital care	Died about 2 weeks after detection of tbc.	Dead	No
Tuberculous pleurisy	Pleural exudate	Hospital care	Regression	Good	—
Tuberculous pleurisy in 1936	Pleural exudate	Hospital care	Regression	Good	—
Bovine primary infection of abdomen, tuberculous peritonitis	Mesenterial lymph node	Hospital care	Died some weeks after onset of the disease	Dead	Yes

Cont inued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
17	M	10 mths	Father, groom	Country	Half-brother had lymphom. tbc. colli + tbc. lymphogl. bronchial. (bovine)	Yes	No	Yes	—
18	F	15 mths	Father, unskilled labourer	Country	Mother and 2 sisters showed evidence of previous abdominal tbc. (calc.)	Yes	No	Yes	—
19	M	3	Father, farmer	Country	—	Yes	No	No	—
20	M	5	Father, farm-labourer	Country	—	Yes	No	No	—
21	F	21	Wife of stone-cutter	Country	—	Yes	Yes	No	—
22	M	17	Metal-worker	Country	—	?	No	No	—
23	M	7	Father, taxi-driver	Town	5 cousins died of pulm. tbc., 4 before patient's birth. The patient seldom met the 5th.	Yes	No	No	—
24	F	4	Father, transport-worker	Town	Paternal grandmother died of pulm. tbc. Paternal aunt has had pulm. tbc., is now non-bacillary. 3 cousins have tbc. (not infectious)	No	No	No	—
25	M	5	Father, farmer	Country	—	Yes	No	No	—
26	M	20	Father, tenant-farmer	Country	Maternal uncle has healed tuberculous spondylitis	Yes	No	No	—

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bovine primary intestinal tuberculosis, tuberculous peritonitis	Mesenterial lymph node; pus in abdomen	Hospital care	Died some weeks after onset of disease (due to perforation of a tuberculous intestinal ulcer)	Dead	Yes
Tbc. of cervical lymph nodes	Stomach washing	Hospital care	Regression	Good	—
Tbc. of cervical lymph nodes	Cervical lymph node	Hospital care. Scraping of liquefied lymphoma	Died 10 months later owing to acute miliary dissemination to various organs	Dead	Yes
Tbc. of tonsils and cervical lymph nodes (primary complex?)	Tonsillar tissue	Hospital care. Tonsillectomy + abrasio, extirpation of lymphomata	Regression	Good	—
Tbc. of cervical lymph nodes	Cervical lymph node	Hospital care. Extirpation of lymphomata	Regression	Good	—
Tbc. of cervical lymph nodes	Punctate from tuberculous cervical node	Hospital care. Extirpation of lymphomata	Regression	Good	—
Tbc. of tonsils and cervical lymph nodes (primary complex?)	Tonsillar tissue	Hospital care. Tonsillectomy	Regression	Good	—
Phlyctena, tbc. of cervical lymph nodes, hilar adenitis and transient infiltration of right lung	Stomach washing	Hospital care	Regression	Good	—
Bone tbc. with abscess	Abscess punctate	Hospital care	Regression	Good	—
Bone tbc. with abscess	Abscess punctate	Hospital care	Died 1 month after detection of disease	Dead	No

Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
27	M	6	Father, manufacturer	Country	—	?	No	No	—
28	F	62	Wife of farmer	Country	—	Yes	Yes	No	Residues of healed primary complex in right lung and hilar region
29	F	29	Living at home. Father, farmer	Country	Brother died from pulm. tbc. 2 years previously (1935). Sister had tuberculous primary complex in 1935	Yes	Yes	No	—
30	M	29	Agent	Town	—	Yes	Yes	No	—
31	F	23	Domestic servant	Country	Father died of pulm. tbc.	Yes	Yes	No	—
32	F	28	Wife of brickyard worker	Country	—	Yes	Yes	No	—
33	F	28	Shop-assistant	Country	—	?	No	No	—
34	M	25	Plumber	Town	—	?	No	No	Signs (calc.) of an earlier tuberculous infection in left lung and hilar region (healed primary complex)
35	M	34	Taxi-driver	Town	Sister died of pulm. tbc.	Yes	No	No	Evidence of old tbc. of abdominal lymph. nodes
36	F	34	Microscopist	Country	—	Yes	No	No	Evidence of old tbc. of abdominal lymph nodes

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bone tbc. with abscess	Abscess punctate	Hospital care	Regression	Good	—
Bone tbc. with abscess	Abscess punctate	Hospital care	Regression. General condition poor, owing to decrepitude	Poor	—
Bone and pulm. tbc. in 1937	Knee-joint punctate	Hospital care	Regression	Good	—
Tbc. of right epididymis	Urine	Hospital care	Stationary	Good	—
Bursitis tbc. tuberosit. tibiae + tbc. renis.sin.	Urine	Hospital care. Nephrectomy	Regression	Good	—
Left-sided renal tbc.	Urine	Hospital care. Left-sided nephrectomy	Later also right-sided renal tbc.	Good	—
Left-sided renal tbc.	Urine	Hospital care. Left-sided nephrectomy	Later also right-sided renal tbc. Died about 4 years after onset of the disease	Dead	No
Bilateral renal tbc.	Urine	Hospital care. Left-sided nephrectomy	Symptom-free	Good	—
Right-sided renal tbc.	Pus from pyonephrosis sac	Hospital care. Nephrectomy	Symptom-free	Good	—
Left-sided renal tbc.	Urine	Hospital care. Nephrectomy	Symptom-free	Good	—

Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
37	M	25	Farm-labourer	Country	—	Yes	Yes	No	—
38	M	32	Building-trade operative	Country	Brother died of bone tbc.	Yes	Yes	No	Signs (calc.) of old healed pulm. tbc. Left-sided exud. pleur. in 1916. Epididymit. et vesiculit. seminal. dx. tbc. in 1934. Left-sided tbc. epididymit. in 1935
39	F	18	Domestic servant	Town	—	Yes	No	No	Erythema nodosum in 1935
40	M	68	Farmer	Country	—	Yes	Yes	No	Diabetes mellitus
41	M	40	Textile worker	Country	—	Yes	No	No	—
42	M	23	Cowman	Country	Paternal aunt has had pleurisy. Father died of pulm. tbc. in 1925. Sister has pulm. tbc. (human T.B.)	Yes	Yes	No	—
43	M	16	Farm-labourer	Country	Sister had erythema nodosum	Yes	Yes	No	—
44	F	26	Typist	Town	—	No	No	No	—
45	M	40	Cowman	Country	Two of brother's children have pulm. tbc. (human T.B.)	Yes	Yes	No	Bilateral exudative pleurisy (bovine T.B.) in 1936

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Right-sided renal tbc.	Urine	Hospital care. Nephrectomy	Symptom-free	Good	—
Bilateral renal tbc. in 1935	Urine	Hospital care	Right-sided exudative pleurisy and diabetes mellitus in 1937	Good	—
Right-sided renal tbc. and right-sided pulm. tbc. (non-cavernous) in 1937	Urine	Hospital care	Lung changes have since progressed a little, but are non-bacillary	Good	—
Bilateral pulm. tbc. (cavernous) (Fig. 11)	Sputum	Hospital care	Condition gradually deteriorated, mostly due to diabetes. Died about 6 months after diagnosing of disease	Dead	No
Bilateral pulm. tbc. (non-cavernous) (Fig. 12)	Sputum	Hospital care	Regression	Good	—
Right-sided pulm. tbc. (cavernous) (Fig. 13)	Sputum	Hospital care	Regression	Good	—
Left-sided pulm. tbc. (non-cavernous)	Stomach washing	Hospital care	Regression	Good	—
Bilateral pulm. tbc. (non-cavernous) (Fig. 14)	Sputum	Hospital care. Bilateral pneumothorax	Progression	Hopeless	—
Bilateral pulm. tbc. (non-cavernous) in 1937 (Fig. 15)	Pleural exudate Sputum	Hospital care. Thoracentesis	Stationary	Fairly good	—



Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
46	M	18	Farm-labourer	Country	—	Yes	Yes	No	Scrofula in 1930
47	F	17	Shop-assistant	Town	Mother died of pulm. tbc. in 1927	Yes	No	No	Suspected pulm. tbc. in 1928, X-ray evidence (calc.) of an old tbc. of hilar lymph nodes
48	F	35	Wife of hospital-attendant	Town	—	Yes	No	No	Diabetes in 1931. Left-sided exudative pleurisy in 1932
49	F	24	Wife of farmer	Town	Sister has bovine primary complex in the lung-hilar region (Case 8)	Yes	Yes	No	Erythema nodosum in 1934
50	M	47	Farm-labourer	Country	—	Yes	No	No	—
51	F	12	Father, farmer	Country	—	Yes	No	No	X-ray evidence (calc.) of an old tbc. of hilar lymph nodes and the right lung
52	F	18	Dress-maker	Town	Paternal aunt treated for exudative pleurisy in 1933	?	No	No	Cervical lymph node tbc. in 1935. X-ray evidence of extensive old tbc. of abdominal lymph nodes
53	F	30	Photographer	Town	—	?	No	No	Tbc. of cervical lymph nodes in 1927. X-ray evidence of old tbc. of abdominal lymph nodes

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bone tbe. and bilateral pulm. tbe. (non-cavernous) in 1935 (Fig. 16)	Stomach washing	Hospital care	Regression	Good	—
Bilateral pulm. tbe. (cavernous) in 1936 (Fig. 17)	Sputum	Hospital care. Bilateral pneumothorax	Regression	Good	—
Right-sided pulm. tbe. (non-cavernous) in 1939 (Fig. 18)	Sputum	Hospital care. Artificial pneumothorax	Regression	Good	—
Right-sided pulm. tbe. (cavernous) in 1938 (Fig. 19)	Sputum	Hospital care. Artificial pneumothorax	Regression	Good	—
Bilateral pulm. tbe. (cavernous) (Fig. 20)	Sputum	Hospital care	Steady progression. Died about 5 months after diagnosis of disease	Dead	No
Right-sided pulm. tbe. (non-cavernous) (Fig. 21)	Sputum Lung tissue	Hospital care. Artificial pneumothorax	Steady progression. Later tbe. of both lungs and of intestines. Died about 11 months after detection of disease	Dead	Yes
Left-sided pulm. tbe. (non-cavernous) in 1936 (Figs. 22—23)	Sputum Various necropsy material	Hospital care. Artificial pneumothorax	Lung changes soon became cavernous. Steady progression. Died about 9 months after diagnosis of pulmonary affection	Dead	Yes
Bilateral pulm. tbe. (cavernous) in 1936	Sputum	Hospital care. Bilateral pneumothorax	Regression	Good	—

Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living in	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest
54	M	16	Agricultural worker	Country	Two cousins of the father died of pulm. tbc.	Yes	Yes	Yes	—
55	M	21	Painter	Town	—	?	No	No	X-ray evidence of an old tbc. of the abdominal lymph nodes
56	F	25	Milkmaid	Country	Brother treated for tbc. lymphogl. mediast. et mesenter. in 1937	Yes	Yes	Yes	—
57	F	42	Wife of tenant-farmer	Country	Father died of pulm. tbc. in 1898	Yes	Yes	No	—
58	F	22	Living at home. Father, farmer	Country	—	Yes	Yes	No	—
59	F	38	Wife of farmer	Country	Brother and sister died of pulm. tbc. in 1933 and 1937 respectively.	Yes	Yes	No	—
60	F	52	Wife of farmer	Country	Husband had pulm. tbc. in 1927	Yes	Yes	No	Right-sided pleurisy in 1909
61	F	20	Living at home. Father, farmer	Country	Two first cousins died of tbc. in 1927 and 1934 respectively	Yes	No	No	—

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bilateral pulm. tbc. (cavernous) (Fig. 24)	Sputum	Hospital care. Artificial pneumothorax	Regression	Good	—
Left-sided pulm. tbc. (cavernous) (Fig. 25)	Sputum	Hospital care. Artificial pneumothorax. Cauterisation of adhesions	Steady progression. Soon bilateral pulm. tbc. and cervical tbc. Died 7 months after diagnosis of the lung disease	Dead	Yes
Left-sided pulm. tbc. (cavernous) in 1936 (Fig. 26)	Sputum	Hospital care. Intrapleural later extrapleural pneumothorax treatment	Steady progression of changes to both lungs and to intestines. Died about 17 months after detection of the disease	Dead	No
Right-sided pulm. tbc. (cavernous) (Fig. 27)	Sputum	Hospital care. Artificial pneumothorax	Slow progression in both lungs. Lived for about 10 years after detection of the disease	Dead	Yes
Right-sided pulm. tbc. (cavernous) (Fig. 28)	Sputum	Hospital care. Artificial pneumothorax and cauterisation of adhesions	Regression	Good	—
Left-sided pulm. tbc. (cavernous) (Fig. 29)	Sputum	Hospital care. Bilateral pneumothorax	Steady progression of changes in both lungs. Later the affection spread to the tendon sheaths, to larynx and possibly also to kidneys. Died about 17 months after detection of disease	Dead	No
Right-sided pulm. tbc. (cavernous) in 1936 (Fig. 30)	Sputum	Hospital care	Died about 5 months after diagnosis of the pulmonary affection	Dead	No
Right-sided pulm. tbc. (cavernous) (Fig. 31)	Sputum	Hospital care. Artificial pneumothorax and cauterisation of adhesions	Steady progression in both lungs, later also intestinal tbc. Died about 1 year and 9 months after diagnosis of pulmonary affection	Dead	No

Continued

General anamnestic data									
Case No.	Sex	Age	Occupation	Living In	Family History	Drank raw milk	Milked	Source of infection traced	Previous illness of interest.
62	F	24	Wife of farm-labourer	Country	—	Yes	Yes	No	Signs of earlier tbc. of cervical and axillary lymph nodes
63	F	21	Dress-maker	Country	Paternal grandmother died of pulm. tbc. in 1891. Father has healed tuberculous primary complex	Yes	Yes	No	—
64	M	25	Farm-labourer	Country	—	Yes	No	No	Diabetes mellitus
65	F	31	Wife of farm-labourer	Country	One child has tbc. of the cervical lymph nodes	Yes	Yes	No	—
66	F	19	Wife of farm-labourer	Country	Maternal aunt had pulm. tbc. in 1935 (pat. has not met her for 8 years). Only child, 3 years old, shows signs of tuberculous infection (positive tuberculin reaction)	Yes	Yes	No	—
67	M	68	Farmer	Country	—	Yes	Yes	No	Evidence of old tbc. of abdominal lymph nodes

Onset and course of the bovine tuberculosis					
Diagnosis on detection of disease	Bovine tubercle bacilli shown in	Treatment	Course of disease	Present condition	Necropsy
Bilateral pulm. tbc. (cavernous) and laryngeal tbc. (Fig. 32)	Sputum	Hospital care	Steady progression. Died about 9 months after detection of pulmonary affection	Dead	No
Left-sided pulm. tbc. (cavernous) (Fig. 33)	Sputum	Hospital care. Artificial pneumothorax, cauterisation of adhesions, phrenic evulsion	Steady progression in both lungs, later also renal tbc. Died about 1 year and 10 months after diagnosis of the pulmonary affection	Dead	No
Left-sided pulm. tbc. (cavernous) (Fig. 34)	Sputum	Hospital care. Artificial pneumothorax	Steady progression in both lungs. Later also right-sided spontaneous pneumothorax. Died about 10 months after detection of the disease	Dead	No
Left-sided pulm. tbc. (cavernous) (Fig. 35)	Sputum	Hospital care, artificial pneumothorax and oleothorax treatment	Steady progression in both lungs. Developed also laryngeal tbc. Died about 3 years after detection of lung disease	Dead	No
Bilateral pulm. tbc. (cavernous) in 1937 (Fig. 36)	Sputum	Hospital care, bilateral pneumothorax, right cauterisation of adhesions	Steady progression in both lungs, later intestinal tbc. developed. Died about 1 year after detection of pulmonary affection	Dead	No
Bilateral pulm. tbc. (cavernous), laryngeal and intestinal tbc. (Fig. 37)	Sputum Mesenterial lymph node	Hospital care	Steady progression. Died already 2 weeks after detection of disease	Dead	Yes

to the different groups primary importance has been attached to the principal tuberculous manifestation.

The figures in brackets (Table 6) denote the number of new cases of bovine tuberculosis in man detected after the conclusion of the present investigation. These cases, which do not differ in any way from those observed earlier, will be omitted from our discussion. On the other hand, a detailed account will be given of the 67 cases.

Table 6.

Group		No. of cases	New cases	Total
1.	No demonstrable changes, but bovine T.B. present in the gastric lavage (Case 1) ....	1	(1)	2
2.	Hilar or lung changes (or both), occurring in association with or shortly after the primary infection (Cases 2—10) .....	9	(3)	12
3.	Miliary tuberculosis and tuberculous meningitis (Cases 11—12) .....	2	(0)	2
4.	Tuberculous meningitis (Case 13) .....	1	(1)	2
5.	Tuberculous pleurisy (Cases 14—15) .....	2	(2)	4
6.	Tuberculous peritonitis (Cases 16—17) .....	2	(1)	3
7.	Tuberculosis of cervical lymph nodes; tuberculous tonsillitis (Cases 18—24) .....	7	(5)	12
8.	Bone tuberculosis (Cases 25—29) .....	5	(4)	9
9.	Urogenital tuberculosis (Cases 30—39) .....	10	(2)	12
10.	Pulmonary tuberculosis (Cases 40—67) .....	28	(8)	36
Total		67	(27)	94

Each group of cases will be treated separately. A description of the symptoms and the changes at the time of diagnosis is given in Table 7, and a summary of the further development of the changes and the treatment given will be found in Table 5.

*Group 1 consists of cases without any demonstrable changes, but in whom tubercle bacilli were found in the gastric lavage.* In cases belonging to this group the possibility of the bovine tubercle bacilli originating from recently ingested milk must be excluded. The patients must also be tuberculin positive. Only one case, Case 1, has been referred to this group, viz. that of a girl who was examined because her mother had small pulmonary changes of tuberculous

origin, which were, however, stationary and non-bacillary. The girl felt well, but had had a poor appetite for some time past. No morbid changes could be detected. She gave a positive tuberculin reaction, although she was only 4 years of age, and bovine tubercle bacilli were found in the stomach washing. The bacilli could not possibly have originated from recently ingested milk, as they were demonstrated at a hospital, where bacillus-infected milk is of course not supplied. No morbid changes have developed during a period of observation lasting about 3 years. The patient's present health is good.

*Group 2 comprises 9 cases (Cases 2—10) with hilar or lung changes (or both) occurring in association with or shortly after a primary tuberculous infection.* Thus the changes should be due to an *inhalation* of bovine tubercle bacilli. This interpretation must be regarded as rather remarkable. Only a relatively short time ago the generally accepted view was that bovine tuberculosis in man was due to the ingestion of food, especially milk, containing tubercle bacilli. The primary infection therefore developed nearly always in the abdomen, sometimes in the tonsils and the adjacent cervical lymph nodes. Starting from these locations, the further bacillary spread took place especially along the haematogenous route. The possibility of an aerogenous infection, as in human tuberculosis, was overlooked for quite a long time. Now we know, however, that bovine infection can also take place by inhalation of the bacilli; but this mode of infection is generally considered to be rare. *The occurrence of not less than 9 such cases in a material of 67 tuberculous cases is therefore especially noteworthy, as it may go to show that bovine infection by the aerogenous route is much more common than was formerly supposed.* If that is so, a change must be made in our fight against bovine infection. On that account it behoves us to find out what evidence is offered by the different cases in support of the infection being due to an inhalation of bovine tubercle bacilli.

Of the 9 cases 3 were children of the same family, aged 5, 7 and 10 years respectively (Cases 2—4). In 1938 the father, who has a small farm, purchased a cow, which was slaughtered in August of the same year. This animal was found to be affected with «extensive tuberculosis of the lungs, kidneys, udder, scrota and uterus». On the farm there were also two cows which, when slaughtered in



September, were found to have pulmonary tuberculosis. Milk from these cows had been used in the household. *The children used to play in the stall.* In June—July 1938 six of the seven children of this family became ill at about the same time. The only one that remained well was the youngest child aged 7 months, who had been fed on mother's milk or boiled cow's milk. This child was tuberculin negative and had a normal lung radiogram. *All the other children, who were tuberculin negative in the autumn of 1937, now gave a positive tuberculin reaction.* Bovine tubercle bacilli were, however, found in only 3 of these children (Cases 2—4), and they are therefore the only ones included in this series. *All 3 of them had erythema nodosum and hilar adenitis, one of them also showing in addition pulmonary changes,* partly due to tuberculosis, partly to atelectasis (Figs. 1—2). Bovine tubercle bacilli were found in the sputum and in the gastric lavage in 2 of the cases, but only in the gastric lavage in the third case. In these cases there can hardly be any doubt that the infection was air-borne, and that erythema nodosum and hilar-lung changes of exactly the same appearance as in human primary infections developed as a direct result of the primary infection. If the bacilli had not been bovine, there would certainly have been no question of the primary lesion having any other location than that mentioned.

In the next case (Case 5), too, there cannot be much doubt as to the origin of the intrathoracic changes in immediate association with a bovine primary infection. The source of infection was a cow, which was found to have extensive tuberculosis when slaughtered in March 1937. At about the same time the patient had *erythema nodosum and the radiogram revealed the presence of a primary complex* (tuberculous changes in the left lung and in the left hilar region). Bovine tubercle bacilli were found in the stomach washing. The infectiosity of the cow is also evident from the fact that 3 other children of the family fell ill at the same time, manifesting symptoms of the same disease. One of them had erythema nodosum, another erythema nodosum and a right-sided primary complex, while the third showed symptoms of tuberculosis of the abdominal lymph nodes. *All the children had consumed raw milk from the farm, and they used to play in the cow-house.* However, as no tubercle bacilli could be shown in the 3 last-mentioned cases they have not been in-

cluded in this series, although we have certainly here — as in the preceding cases — to do with a small epidemic of bovine cases.

The next case (Case 6), that of a farm-labourer, aged 29, who had milked cows and consumed raw milk, is not so clear. In this case the source of infection could not be discovered. At Christmas-time, 1938, the patient had a cough, scanty expectoration and stabbing pains in the breast, particularly behind the sternum. A radiographic examination in February 1939 revealed the presence of an extensive right-sided hilar adenitis and parenchymal changes in the posterior part of the right lower lobe (Fig. 3). The rate of sedimentation was greatly increased, 113 mm. Bovine tubercle bacilli were found in the sputum and in the gastric lavage. The further development of the changes was the same as in a primary complex. Regression took place without artificial pneumothorax treatment. *In this case the appearance of the changes at the onset of the disease as well as their development point to a fresh acrogenous infection.* The fact that the source of infection could not be discovered, however, renders the interpretation of the nature of the case somewhat uncertain.

On the other hand, there cannot be any doubt as regards Case 7, that of a boy aged 14, who had milked a cow with open pulmonary tuberculosis. *The changes consisted of a left-sided hilar adenitis and left-sided pulmonary lesions, probably due to a great extent to atelectasis (Figs. 4—5). On the appearance of the changes the patient was tuberculin negative, but soon became positive.* Bovine tubercle bacilli were found in the sputum and in the gastric lavage. At first the changes regressed slowly, but about a year after the onset of the affection the patient died from a tuberculoma of the cerebellum. *The autopsy confirmed the view of the intrathoracic localisation of the primary lesion.*

Case 8 has already been described (see p. 110). *The source of infection in this case was an elder sister with cavernous phthisis. The changes following the primary infection consisted of erythema nodosum and a left-sided primary complex (Figs. 6—7).* Bovine tubercle bacilli were present in the gastric lavage. The mode of infection was undoubtedly acrogenous.

Case 9 was a student at the Veterinary College, Stockholm. In

his practical work as well as at the laboratory he came into contact with tuberculous material. In this case, too, the patient developed *lung and hilar changes* (primary complex) *in addition to erythema nodosum*. Bovine tubercle bacilli were found in the sputum. The connexion between the source of infection and the primary changes can be considered to be rather certain. Aerogenous infection must also have taken place in this case.

Finally, in Case 10 even *post-mortem evidence* was obtained *that the primary focus was situated in the left lung and hilar region, and that the pathway of infection must have been aerogenous*. The source of infection was a cow with extensive tuberculosis. A *left-sided primary complex* developed (Figs. 8—9). The changes progressed rather rapidly, and gradually the process spread haematogenously to different organs of the body. The patient died about 13 months after the disease had been diagnosed. Bovine tubercle bacilli were found in the lung and in the pleural exudate. The autopsy revealed the presence of a caseous primary tuberculosis in the left lung-hilar region.

*Thus, of the 9 cases (Cases 2—10) 8 were in all probability due to the inhalation of bovine tubercle bacilli, and in the remaining case (Case 6) infection may have taken place by the same aerogenous route. In one of the cases, Case 8, the infection was transmitted from one human being to another. Thus the inhalation of bovine tubercle bacilli obviously takes place much more frequently than was formerly supposed. In fact, three more such cases have been observed since the conclusion of this investigation (Table 6).*

A feature of particular interest is that adults are also exposed to bovine primary infection. Thus of the 9 cases 4 were 16, 23, 29 and 30 years of age respectively.

*All patients with a bovine primary infection and fresh lung-hilar changes felt ill in some way or other (Table 7). In not less than 6 of the 9 cases erythema nodosum occurred, which is thus a significant symptom not only in human but also in bovine primary infection. Cough, fatigue and fever were also common symptoms. In solitary cases transient abdominal trouble also occurred, which may have been due to the lowered general condition and the fever caused by the primary infection. In one or two cases there also occurred stitches or stabbing pains in the chest. The rate of sedimentation*

was almost regularly greatly increased, generally between 30 and 50 mm, in one case as high as 113 mm.

In 7 of the 9 cases pulmonary and hilar changes were present simultaneously (primary complex) at the time the disease was diagnosed. In two of these cases the radiographic examination revealed also evidence of atelectasis (Cases 2 and 7; Figs. 1, 4, 5). The other two cases had at first only hilar adenitis. The changes were found somewhat more frequently on the left side than on the right. Radiologically the changes presented the same picture as those following human primary infections. *Thus it cannot be determined from the radiograms whether the primary infection is of human or bovine origin.*

All cases belonging to this group were given the usual hygienic-dietetic treatment at a hospital. One of them (Case 10) also received pneumothorax treatment owing to the rapid progress of the changes. Two of the cases died about one year after the affection had been diagnosed, one (Case 7) as the result of a bovine tuberculoma of the cerebellum, the other (Case 10) owing to a haematogenous spread of the disease to other parts of the body. Further, in one case (Case 4) tuberculous changes appeared centrally in the left lung about a year later. The changes regressed rather soon however. Since then no new tuberculous manifestations have occurred either in this case or in the other 6 surviving cases. It will of course be of great interest to follow these cases for a long period of years in order to learn how the bovine tuberculosis will develop in future. As to the prognosis nothing can of course be said for certain at present. So far the cases are not better or worse than those caused by human tubercle bacilli.

*Group 3 consists of 2 cases of milary tuberculosis and tuberculous meningitis (Cases 11 and 12), and Group 4 of 1 case of tuberculous meningitis (Case 13).* All three cases were children. The source of infection was discovered in only Case 12. At the age of 8—13 months, i. e. for a period of 6 months, the patient was fed on raw milk from 3 cows with open tuberculosis. Bovine tubercle bacilli were found in the cerebrospinal fluid from all three children. In 2 cases primary lesions occurred in the abdomen, whereas in one case (Case 13) the primary foci could not be found. No autopsy could be performed in the latter case, as the patient died at home.

Still the primary complex was in all probability situated intra-abdominally, for the patient had been troubled with vomitings, loose stools and wasting for a long time before the onset of the meningitis. *The symptoms and the clinical picture were identical with those in miliary tuberculosis and meningitis of human origin.* All three cases died shortly after the onset of the disease. Autopsies were performed on Cases 11 and 12, which revealed, in addition to a bovine primary tuberculosis of the abdomen, also miliary tuberculous changes in various organs as well as tuberculous meningitis.

*Group 5 contains 2 cases of bovine exudative pleurisy (Cases 14 and 15).* Pleurisy occurred, however, also in 4 cases belonging to other groups, and preceded the changes in which bovine tubercle bacilli were found later (Cases 38, 45, 48 and 60). It is probable of course that these pleurisies, like the subsequent changes, were bovine. But this is not absolutely certain except as regards Case 45, in which bovine bacilli were also found in the pleural fluid. In the other cases the bacilli were not typed, as the investigation had not been started at that time. In Case 38 there was an interval of 19 years between the exudative pleurisy and the development of the bovine tuberculous changes, in Case 48 there was an interval of 7 years, and in Case 60 not less than 27 years. It is of course theoretically conceivable that the bovine tuberculosis was preceded by a human tuberculosis, which had regressed and healed. It is much more probable however, provided that the pleurisy was of tuberculous origin, that the same bovine strain was the cause of all the morbid changes.

The 3 cases of pleurisy of certain bovine origin (Cases 14, 15 and 45) occurred in adults. In two cases the pleural effusion was on the left side, in the third case (Case 45) it was bilateral and was followed by a bilateral haematogenous tuberculosis about a year later (Fig. 15). In all three cases bovine tubercle bacilli were found in the pleural exudate, in Case 45 also in the sputum. The source of infection was discovered only in as far as Case 14 was concerned, and was found to be 3 cows with open tuberculosis, which the patient had tended and milked. But owing to a distaste for milk she had not drunk any milk for more than 15 years. It is therefore probable that in this case too, the infection was aerogenous. The infection was also air-borne in Case 15. About 17 months before the onset

of the pleurisy this patient had erythema nodosum, a primary complex in the right lung and incipient tuberculous changes at the left apex. Although no tubercle bacilli could be demonstrated until the development of the pleural effusion, there is hardly any doubt that the erythema nodosum and the primary complex, which were followed by pleurisy shortly afterwards, were caused by one and the same bovine virus.

*The clinical picture agrees in every respect with that of exudative pleurisy of human origin.* The symptoms were those usually met with in the latter disease, the sedimentation rate being also greatly increased.

The subsequent development of the disease was somewhat different in the 3 pleurisy cases. Two of them (Cases 14 and 15) gradually improved. No new tuberculous manifestations have occurred during an observation period of more than 5 years. On the other hand, in the third case (Case 45) the affection became progressive already about 1 year later. Bilateral, haematogenous changes developed in the lungs. Bovine tubercle bacilli were now also present in the sputum. For the last year or two, however, the changes have remained stationary. The patient's general condition is fairly good.

*Group 6 is represented by 2 cases affected with tuberculous peritonitis* (Cases 16 and 17). Both cases were infants, aged 16 and 10 months respectively, who had fever and loose stools — Case 16 had also a cough and loss of appetite. The rate of sedimentation was greatly increased, 25 and 36 mm respectively. Exudate was shown in the abdomen. Both patients died after a few weeks' illness, Case 17 due partly to a perforation of one of the tuberculous abdominal ulcers and secondary peritonitis. Bovine tubercle bacilli were present in the mesenterial lymph nodes, in Case 17 also in pus from the abdomen. The post-mortem examination revealed in Case 16 the presence of a serous exudate in the abdomen. The abdominal viscera had fused together into one single packet. The mesenterial lymph nodes were swollen and had a white, fatty cut surface. The retroperitoneal lymph nodes, on the other hand, were normal. In Case 17 numerous tuberculous mucous membrane ulcers, sometimes in the form of rings, were found, particularly in the lower part of the ileum. One of these ulcers had perforated.

Table 7.  
Symptomology and changes at the time of diagnosis.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
1	Bovine tuberculous infection	Loss of appetite	10	No demonstrable changes.
2	Erythema nodosum, hilar adenitis and pulmonary tbc. (primary complex)	Cough, vomitings, poor appetite, fever, <i>erythema nodosum</i>	37	Bilateral hilar adenitis. Evidence of enlarged mediastinal lymph nodes. Three weeks later a compact density was discernible in the left apical field (Fig. 1).
3	Erythema nodosum and hilar adenitis	Cough, fatigue, stomach-ache, loose stools, poor appetite, fever, <i>erythema nodosum</i>	29	Right-sided hilar adenitis (Fig. 2), small right-sided pleural exudation; later also left-sided hilar adenitis and signs of enlarged mediastinal lymph nodes.
4	Erythema nodosum and hilar adenitis	Cough, fatigue, pain in stomach, loose stools, fever, <i>erythema nodosum</i>	45	Left-sided hilar adenitis.
5	Erythema nodosum, hilar adenitis, pulm. tbc. (primary complex)	Fatigue, stomach-ache, fever and <i>erythema nodosum</i>	9	Left-sided hilar adenitis and small parenchymal change just below left hilum.
6	Hilar adenitis and pulm. tbc. (primary complex)	Cough, scanty expectoration, stitch in the chest, especially behind the sternum	113	Right-sided hilar adenitis, also parenchymal changes of spotty appearance in posterior part of right lower lobe (Fig. 3).
7	Hilar adenitis and pulm. tbc. (primary complex)	Fatigue, stitch in left side of chest, cough, fever	50	Left-sided hilar adenitis, parenchymal change (also atelectasis) in the form of a compact density at base of left lung. Regression later (Figs. 4—5).
8	Erythema nodosum, hilar adenitis, pulm. tbc. (primary complex)	Fever, <i>erythema nodosum</i>	50	Left-sided hilar adenitis (Fig. 6); two months later also a small mottled parenchymal opacity below and behind the left hilum (Fig. 7).
9	Erythema nodosum, hilar adenitis, pulm. tbc. (primary complex)	<i>Erythema nodosum</i>	Increased	Right-sided hilar adenitis, spotty parenchymal density below and behind the hilum.
10	Hilar adenitis, pulm. tbc., tbc. of mediastinal lymph nodes (primary complex)	Cough, fatigue, emaciation, stitch in the left side of the back	36	Left-sided hilar adenitis, parenchymal density, as large as a walnut, centrally in the left lung, enlarged mediastinal lymph nodes (Figs. 8—9).

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
11	Bovine primary tbc. of abdomen, acute miliary tbc. and tuberculous meningitis	Fatigue, vomitings, poor appetite, headache, photophobia, fever	—	Grain-sized mucous membrane ulcer in jejunum. Corresponding mesenterial lymph nodes caseously yellowish white. Tuberculous meningitis. Miliary tuberculous foci in lungs, liver, spleen and kidneys (Fig. 10).
12	Bovine primary tbc. of abdomen, acute miliary tbc. and tuberculous meningitis	Attacks of cramp and periods of apathy	—	Mesenterial lymph nodes as large as walnuts, partly changed into a caseous mass. Tuberculous meningitis. Miliary tuberculous foci in pleura, liver and spleen.
13	Tuberculous meningitis	Vomitings, wasting, loose stools, fever	15	Tuberculous meningitis.
14	Tuberculous pleurisy	Fatigue, fever, stitch in left side of chest, later also dyspnoea and cough	83	Radiogram showed large exudate shadow on left side, but no lung changes.
15	Tuberculous pleurisy	Shivering-fits, dry cough, no stitch	—	Radiogram showed large exudate shadow on left side and residues of an earlier left-sided apical pulm. tbc.
16	Bovine primary infection of abdomen, tuberculous peritonitis	Cough, fever, poor appetite, loose stools, slight pain in the chest	25	Exudate in peritoneal cavity. Caseous coatings between intestinal folds. Mesenterial lymph nodes swollen and had white, fatty cut surface.
17	Bovine primary intestinal tuberculosis, tuberculous peritonitis	Fever, loose stools	36	Numerous tuberculous ulcers in intestinal mucosa, especially in lower part of ileum. Tuberculous mesenterial lymph nodes. Tubercles in peritoneum.
18	Tuberculosis of cervical lymph nodes	No general effects. Trouble only from nodes	32	Lymph nodes varying in size from hazel-nut to plum on neck, also far up on nape.
19	Tuberculosis of cervical lymph nodes	No general effects	—	At first a packet of lymph nodes the size of a hazel-nut, soon increasing to that of pigeon's eggs, on the neck.
20	Tuberculosis of tonsils and cervical lymph nodes (primary complex?)	No general effects	10	Packet of enlarged lymph nodes, the size of a hen's egg, on the neck, also hypertrophy of the tonsils.



Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
21	Tuberculosis of cervical lymph nodes	No general effects	15	Walnut-sized node on neck.
22	Tuberculosis of cervical lymph nodes	No general effects	19	Enlarged lymph nodes on the neck, which recurred again and again.
23	Tuberculosis of cervical lymph nodes and tonsils (primary complex?)	No general effects	—	Enlarged lymph nodes on neck; enlarged tonsils.
24	Phlyctena, tuberculosis of cervical lymph nodes, hilar adenitis, transient pulmonary infiltration	Phlyctena	12	Enlarged lymph nodes, containing calcifications, on neck. Right-sided hilar adenitis and right-sided central parenchymal density, which soon disappeared.
25	Bone tuberculosis with abscess	Limp in right leg, pain in right knee	30	Tuberculosis of the right hip-joint with abscess.
26	Bone tuberculosis with abscess	Pain from an gluteal abscess	50	Walnut-sized tuberculous focus in posterior part of the os ileum. Tuberculous abscess.
27	Bone tuberculosis with abscess	Fatigue, poor appetite, fever, vomitings, wasting, poor gait, weakness and pain in right leg	59	Tuberculosis of the right trochanter with abscess.
28	Bone tuberculosis with abscess; (residues of tuberculous affection in right lung-hilar-region.)	Aching, swollen and reddened right elbow-joint	—	Tbc. epicond. med. humeri dx.; 5 years later tbc. cubiti dx. e. abscess.
29	Bone and pulmonary tuberculosis	Pain in swollen right knee-joint	25	Tuberculosis of knee-joint. Several very large parenchymal foci centrally in left lung.
30	Tuberculosis of right epididymis	Secretion from fistula	7	Hen's egg-sized resistance in right scrotal half, in the front part of which the testis could be demarcated. A fistula orifice was found on the outside of the scrotum.
31	Bursit. tbc. tuberosit. tibiae + tbc. ren. sin.	Frequent urinations; troublesome ache in left side of abdomen, radiating out towards back and down towards urethra	5	Lowest papilla of kidney was ulcerated. Some non-liquefied tubercles in relative pyramid.
32	Left-sided renal tuberculosis	Frequent and painful urinations, red-coloured urine, ache above left hip-joint	—	At first left-sided, later bilateral renal tuberculosis. Upper part of left kidney, which was removed, showed extensive cavernous lesions.

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
33	Left-sided renal tuberculosis	Frequent urinations, severe attacks of pain in left side of back	58	At first left-sided, later bilateral renal tuberculosis. Parenchyma of left kidney, which was removed, was dotted with tubercles.
34	Bilateral renal tuberculosis; (residues of tuberculous affection in left lung-hilar region)	Pain in left side of abdomen, radiating towards back	41	Left kidney interspersed with cavities, up to the size of Spanish nuts, containing caseous matter. Besides, old and fresh tuberculous changes could be observed. Tuberculous ulceration occurred in the left ureter.
35	Right-sided renal tuberculosis; (residues of an old. tbc. of abdominal lymph nodes)	Tired, loss of appetite, stitch in right side of chest, fever	96	Nephrectomy showed a large pyonephrotic kidney. The sac was composed of partly caseous granulation tissue, containing tubercles. Abundant calcified lymph nodes in the abdomen.
36	Left-sided renal tuberculosis; (residues of old tbc. of abdominal lymph nodes)	Relapsing cystitis	50	The kidney was interspersed with a large number of caseous tuberculous cavities. Calcified lymph nodes in the abdomen.
37	Right-sided renal tuberculosis	Right-sided renal colic, bladder trouble	3	About the middle of the kidney there was a hazel-nut-sized, nearly infarct-like area with dense, partly caseous miliary nodules. Tuberculous nodules were also found in the right ureter.
38	Bilateral renal tuberculosis; (residues of an old pulm. tbc. and rests of a bilateral pleurisy)	Bladder-trouble	18	Nephrectomy has not been performed. Calcified spots could be observed in the left supraclavicular region. Rests of left-sided pleurisy.
39	Right-sided renal tuberculosis, right-sided pulm. tbc.	Fatigue, fever	21	Nephrectomy has not yet been performed. A mottled density could be seen in the right ScI—II, which coalesced into a spot hardly the size of a hazel-nut.
40	Bilateral pulm. tbc. Diabetes mellitus	Fatigue, wasting, thirst, unsteadiness on feet, dyspnoea	52	Centrally in left lung field there was a slightly striated and somewhat mottled shadow the size of the palm of a man's hand, and behind the right C <sub>6</sub> a scarcely walnut-sized cloudy spot with central rarefaction (cavity) (Fig. 11).

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
41	Bilateral pulm. tbc.	Cough, expectoration, hoarseness, night sweats, poor appetite wasting and fever	35	In both apical fields there was a mottled density and pleural coating. The changes were somewhat more pronounced on the right side. A mottled density could also be seen at the base of the left lung. No cavity. (Fig. 12).
42	Right-sided pulm. tbc.	Cough, haemoptysis headache	6	A cloudy opacity with central rarefaction (cavity) in the right supraclavicular region (Fig. 13).
43	Left-sided pulm. tbc.	Subjectively healthy	26	A walnut-sized cloudy shadow occurred in the left III, the left hilar shadow was somewhat enlarged and condensed. Striae could also be discerned in the left II—III. No cavity.
44	Bilateral pulm. tbc.	Cough, expectoration	82	Mottled, cloudy, parenchymal changes with bronchiectasis in the right ScI—III and mottling and more striated shadows in the left ScI—I. No cavity. (Fig. 14).
45	Bilateral bovine exudative pleurisy; one year later bilateral bovine pulm. tbc.	Fatigue, poor appetite, wasting, dry cough, dyspnoea; fever	21	Mottled parenchymal density in upper one-third of both lungs. No cavity. Pleural rests of earlier bovine pleurisy basally on both sides. (Fig. 15).
46	Bone tbc., bilateral pulm. tbc.	Pain in right ankle-joint	47	Tbc. ped. dx. In right upper field there was a faint parenchymal density. A striated density extended from the left hilum up towards a cloudy shadow, an inch in size, in the left supraclavicular region. A diffuse opacity could also be seen within a limited area in the centre of the left lung. Rests of right-sided pleurisy. No cavity. (Fig. 16).
47	Bilateral pulm. tbc; (residues of old tbc. of hilar glands)	Cough, expectoration, fatigue, fever	30	A cloudy opacity, the size of the palm of the hand, behind C <sub>1</sub> and I <sub>1</sub> on the right side, and a rarefaction in the centre of this area (cavity). A pleural coating, and calcifications in the hilar region could be seen on the left side (Fig. 17).

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
48	Right-sided pulm. tbc. Diabetes mellitus	Subjectively healthy	25	A mottled, partly confluent density in the right upper lobe, mostly pronounced in C <sub>I</sub> —III. No cavity. Rests of left-sided pleurisy (Fig. 18).
49	Right-sided pulm. tbc.	Cough, sputum, hoarseness, poor appetite, wasting, fatigue, stitch in right side of chest.	66	A cavity as large as a plum immediately outside the right hilar region. (Fig. 19).
50	Bilateral pulm. tbc.	Cough, poor appetite, wasting, fatigue, night sweats	75	Extensive tuberculous changes in entire left lung, and an orange-sized cavity at the apex. Less pronounced tuberculous changes in the right lung. (Fig. 20).
51	Right-sided pulm. tbc. (rests of earlier tbc. of hilar lymph nodes and apical tbc.)	Cough, fatigue, fever	49	Within the upper two-thirds of the right lung there was a cloudy, spotty, mostly confluent parenchymal density. The right hilar shadow was enlarged. Calcifications could be seen in the right hilar region, also at the apex of the right lung. Rests of left-sided pleurisy. No cavity. (Fig. 21).
52	Left-sided pulm. tbc. (rests of tbc. of abdominal lymph nodes and tbc. of right hilar nodes and cervical nodes)	Cough, expectoration, fatigue, fever, stitch in left side of chest	53	A compact density in lower half of left lung. Left hilar shadow was considerably enlarged and condensed (Fig. 23). No cavity (later however cavernous liquefaction of the pneumonic area). Abundant calcified nodes in abdomen (Fig. 22) Tuberculous cervical lymph nodes.
53	Bilateral pulm. tbc. (rests of an earlier tbc. of abdominal and cervical lymph nodes)	Cough, fatigue, wasting, fever	—	A pneumonic consolidation with a hazel-nut-sized cavity centrally in the upper one-third of right lung. Cloudy spots could also be seen in the left apical and upper fields. Calcified lymph nodes in the abdomen. Rests of earlier tbc. of cervical lymph nodes.
54	Bilateral pulm. tbc.	Haemoptysis	36	A confluent cloudy opacity in upper one-third of left lung and a hazel-nut-sized cavity on a level with C <sub>II</sub> . A striate density could also be seen in the right I <sub>I</sub> . (Fig. 24).

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
55	Left-sided pulm. tbc; (rests of an old tbc. of abdominal lymph glands)	Haemoptysis	60	A confluent cloudy density in the upper half of left lung, and a walnut-sized cavity on a level with CII. (Fig. 25). Calcified lymph nodes in the abdomen.
56	Left-sided pulm. tbc.	Cough, fatigue	24	A partly confluent, cloudy opacity between CI and III on left side, and a walnut-sized cavity laterally in I. (Fig. 26).
57	Right-sided pulm. tbc.	Cough, wasting, night sweats, stitch in the right side of the chest	—	A confluent cloudy opacity in the upper half of right lung, and a cavity as large as a walnut in the right I. (Fig. 27).
58	Right-sided pulm. tbc.	Cough, sore throat, fatigue, stitch in right side of chest	56	A compact density with a walnut-sized cavity centrally in the right supraclavicular region. Mottling could also be observed medially to the density right down towards the hilum. (Fig. 28).
59	Left-sided pulm. tbc.	Stitch in left side of the chest, fever	62	A compact density the size of a hazel-nut, with central rarefaction (cavity), immediately outside the upper part of the left hilar region (Fig. 29).
60	Right-sided pulm. tbc; (residues of right-sided pleurisy)	Fatigue, giddiness, loss of appetite, wasting	123	Considerable right-sided pleural coating with great displacement of heart and mediastinum to the right. Tuberculous changes and cavity as large as a mandarin in upper part of right lung field (Fig. 30).
61	Right-sided pulm. tbc.	«Influenza» with cough, fatigue, fever, headache	—	A mottled, partly confluent parenchymal density in upper part of right lung, and a cavity nearly as large as a hen's egg in the right Sel—I. (Fig. 31).
62	Bilateral pulm. tbc. and laryngeal tbc; (residues of extensive tbc. of cervical and axillary lymph nodes)	Cough, hoarseness, fatigue, night sweats, wasting, dyspnoea, stitch in right side of chest, vomitings	79	A spotty, highly confluent parenchymal density in the lower two-thirds of the right lung field and a cavity as large as a mandarin in the upper one-third of the same lung. Extensive tuberculous changes occurred also in the lower two-thirds of the left lung in the form of spots, here and there coalescing. Abundant calcified lymph nodes could be seen on the neck and in the axillae. (Fig. 32).

Continued.

Case	Diagnosis	Symptoms	Sed. rate	Extent and appearance of changes
63	Left-sided pulm. tbc.	Cough, fatigue, loss of appetite, wasting, and night sweats	—	A spotty, here and there confluent, parenchymal density in the entire left lung field. The process rapidly progressed so that already after a month a cavity nearly the size of a hen's egg appeared at the apex of the left lung. (Fig. 33).
64	Left-sided pulm. tbc. Diabetes mellitus	•Cold•, cough, fever	23	A confluent, cloudy mottling in the middle field of the left lung, and a walnut-sized cavity laterally in the left II. (Fig. 34).
65	Left-sided pulm. tbc.	Cough, sputum, hoarseness, stitch in back, fever	—	An almost plum-sized cavity at the apex of the left lung and below it another cavity the size of a hazel-nut. Medially to these cavities a diffuse parenchymal density (Fig. 35).
66	Bilateral pulm. tbc.	•Cold•, nasal catarrh, sore throat, expectoration, fatigue, loss of appetite, stitch in right side of chest	126	Extensive spotty parenchymal densities in both lungs, and two large cavities basally on the right side (Fig. 36).
67	Bilateral pulm. tbc. laryngeal and intestinal tbc. (rests of old tbc. of abdominal lymph nodes)	Cough, expectoration, fatigue, fever, wasting	54	Both lungs covered with spotty, parenchymal densities. A plum-sized cavity could also be seen at the apex of the left lung. Necropsy showed also the presence of an old tuberculosis of the abdominal lymph nodes (Fig. 37).

As was evident from the autopsy, the pathway of infection was by the intestine. The source of infection in both these cases was also discovered. For a period of 4 months Case 16 had been fed on milk from a herd in which a cow was afterwards condemned owing to tuberculosis of the lungs and the udder; and two others had been slaughtered previously on account of pulmonary tuberculosis. Case 17 had for 3 months been given milk from a farm where the clinical examination disclosed that not less than 13 cows were affected with open tuberculosis. It should be pointed out that a

half-brother of the latter patient, who had received milk from the same cows, developed bovine tuberculosis (tbc. lymphogl. region. coll. et bronchial.) Thus in both these cases of tuberculous peritonitis the bovine infection was very severe.

*To Group 7 have been referred 7 cases of tuberculosis of the cervical lymph nodes (Cases 18—24), 2 of which had simultaneously tuberculous changes in the tonsils (Cases 20 and 23) <sup>1</sup>.* In these cases the primary complex was probably localised to the tonsils and the associated cervical lymph nodes. One case (Case 24) had, in addition to tuberculosis of the cervical lymph nodes, also hilar adenitis and a transient pulmonary infiltration and at the time of diagnosis was troubled with phlyctena. Since calcified spots could be shown in the cervical lymph nodes, but not in the enlarged lymph nodes of the hilar region, the cervical lesions were in all probability in this case older than the other tuberculous lesions. Tuberculosis of the cervical lymph nodes occurred also in three other cases, referred to Group 10, viz. Cases 52, 53 and 62. These cases, however, had pulmonary tuberculosis at the same time, bovine tubercle bacilli being found in the sputum. That the tuberculosis of the cervical lymph nodes in the two first-mentioned cases was at least very probably of bovine origin is proved by the fact that the primary focus was found in the abdomen. The presence of numerous calcified lymph nodes at this site at any rate argues strongly in favour of this localisation. In Case 52 the post-mortem examination showed the presence of bovine tubercle bacilli also in the abdominal lymph nodes. In this case the tuberculosis of the lungs and of the abdominal and cervical lymph nodes was therefore only different manifestations of one and the same infection by bovine bacilli.

The frequency of tuberculosis of the cervical lymph nodes was about the same in both sexes. Five of the cases were children, the remaining 2 cases being adults aged 17 and 21 years respectively at the time the disease was diagnosed. The 17-year-old patient, however, had manifested symptoms of disease for the past 3 years. The source of infection was discovered in only one case, Case 18.

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<sup>1</sup> These cases are included in a paper on the treatment of tuberculosis of the cervical lymph nodes by H. WULFF in *Acta Chirurgica Scandinavica* (84), 1941, 343.

In 3 of the cases, viz. Cases 21, 22 and 24, it is impossible to determine the pathway by which the bovine tubercle bacilli entered the body, by the alimentary canal or by inhalation, but in one case, Case 18, infection was most probably food-borne, as bovine tubercle bacilli were found in the gastric lavage but no pulmonary changes could be demonstrated. In fact, several members of the family showed evidence of an earlier bovine (?) tuberculosis of the abdomen (numerous calcified lymph nodes). As already mentioned, in 2 of the cases, Cases 20 and 23, bovine tubercle bacilli were found in the tonsillar tissue, therefore the tonsils were no doubt the portals of entry. Finally, in Case 19 the post-mortem examination revealed the presence of a primary tuberculosis in the cervical lymph nodes. In this case, too, the bacilli most probably entered the body through the tonsils.

Most of the cases of tuberculosis of the cervical lymph nodes were unaffected by their disease, and showed only enlarged lymph nodes varying in size from a hazel-nut to a hen's egg. Case 24, however, suffered from phlyctena. The sedimentation rate was moderately increased. *Clinically the enlarged cervical lymph nodes presented nothing characteristic whereby they could be differentiated from corresponding changes of human etiology.*

Several of the lymph nodes underwent liquefaction. Scraping and extirpation of the lymphomata were performed, which generally brought about an improvement in the patient's condition. Only one of the cases, Case 19, died as the result of a miliary dissemination to different parts of the body. Death took place about 10 months after the appearance of the changes.

*Group 8 consists of 5 cases with bone tuberculosis (Cases 25—29), 3 being males and 2 females. Bone tuberculosis (in one foot) occurred also in Case 46, belonging to Group 10, who at the same time had bilateral pulmonary tuberculosis. Although bovine tubercle bacilli were only found in the gastric lavage, there is hardly any doubt that the two simultaneously active tuberculous manifestations were of one and the same bovine origin.*

Two of the cases of bone tuberculosis in Group 8 were children, aged 5 and 6 years respectively, the others were adults, 20, 29 and 62 years of age respectively. The source of infection was not discovered in any of the cases, nor could the pathway of infection



be established for certain. It is nevertheless probable that in Case 27 the first changes caused by the bacilli were situated in the abdomen, for some months before the bone tuberculosis manifested any symptoms the patient had been suffering from loss of appetite, vomitings and considerable wasting, so that he was finally nothing but «skin and bones». On the other hand, in Case 28 the pathway of infection was in all probability pulmonary, as the radiogram revealed rests of an old primary focus in the right lung and hilar region, but no calcified lymph nodes were found in the abdomen.

The symptoms were those usually met with in bone tuberculosis. The rate of sedimentation was increased. The location of the changes is evident from the diagnoses: Coxit. tbc.dx. (Case 25), tbc. oss. ilei (Case 26), tbc. trochanteri dx. (Case 27), tbc. cubiti dx. (Case 28) and gonit. tbc. dx. (Case 29). In Cases 25—28 an abscess developed from the tuberculous focus. Bovine tubercle bacilli were found in the abscess punctate (Case 25—28), and in the punctate from the knee-joint (Case 29). *The clinical picture of the changes agreed with that of the corresponding lesions due to human tubercle bacilli.*

The course of the disease during treatment was generally favourable. Only one case (Case 26) died as the result of the tuberculous affection. Death took place about 4 months after the detection of the disease. Autopsy was not performed.

*Urogenital tuberculosis is represented in the material by not less than 10 cases (Group 9, Cases 30—39).* Five of the patients were males and five females. The ages of the patients varied in general between 23 and 34 years. The only case that did not belong to this age-group was Case 39. This patient, a girl aged 18, had in addition to renal tuberculosis also small changes almost certainly of a tuberculous nature in the lungs. But as tubercle bacilli were found only in the urine, and as the pulmonary changes, seemingly of less importance, could not be *proved* to be bovine, the case has been referred to Group 9 instead of Group 10, to which it would otherwise belong. The source of infection could not be discovered in any of the cases. In Cases 35 and 36 the path of infection was probably intestinal, for radiograms of the abdomen revealed the presence of calcified abdominal lymph nodes. In Case 35 these

calcified nodes were exceedingly numerous, occurring along the median line right from Th<sub>XII</sub> down to the middle part of the sacrum. On the other hand, in Case 34, in which a calcified primary complex was found in the left lung-hilar region, and in Case 38, having large calcium deposits in the left lung, the route of infection was probably pulmonary, caused by inhalation of tubercle bacilli. This is all the more probable as in Case 38 no calcified lymph nodes could be shown in the abdomen. In this case the different tuberculous manifestations followed each other in quick succession. In 1916 the patient had left-sided exudative pleurisy, in 1934 he was found to have epididymit. et vesiculit. seminal. dx. tbc. (et tbc. renis. dx.?). The radiograms of the lungs revealed, in addition to rests of a left-sided pleurisy, also large calcium deposits in the left supraclavicular region. In 1935 he developed left-sided epididymitis and bilateral renal tuberculosis, and in 1937 right-sided exudative pleurisy. Bovine tubercle bacilli were found in the urine in 1937 and in 1939. In the other cases belonging to this group no clue was obtained as to the pathway of infection.

The location of the urogenital tuberculosis in these cases was as follows: The right epididymis (Case 30), renal tuberculosis and tuberculous bursitis (Case 31), renal tuberculosis (Cases 32—38), renal tuberculosis and pulmonary tuberculosis (Case 39). The tuberculous lesions were at first found in the right kidney in 3 cases, and in the left kidney in 4 cases. In 2 cases both kidneys were affected. *The clinical picture of bovine urogenital tuberculosis agreed in every respect with that of the corresponding disease of human origin.* In some of the cases the rate of sedimentation was very high.

Nephrectomy was performed in 7 of the cases. In Case 31 the tuberculous changes were found to be rather good-natured. The lower renal papilla was ulcerated. Solitary, non-liquefied tubercles were found in the corresponding pyramid. On the other hand, the changes were all the more serious in Cases 32, 34 and 36, all of which showed excavation of the renal parenchyma. In Case 33 the renal tissue was diffusely interspersed with tubercles. Pyonephrosis was observed in Case 35. The sac was partly composed of caseous granulation tissue containing tubercles. Finally, in Case 37 there was in about the middle of the kidney an almost infarct-like

area, the size of a hazel-nut, containing dense, partly caseous miliary nodules. Solitary miliary nodules were also found in the ureter on the same side.

*Thus the changes were generally of a very serious nature and extensive.* Case 32 was later complicated with tuberculosis in the other kidney. A few years later Case 38 developed a right-sided exudative pleurisy. In most of the cases, however, the general condition is at present good. Only one of the cases, Case 33, has died from the disease. Death took place about 4 years after the appearance of the renal changes. There was no necropsy.

*The remaining 28 cases (Cases 40—67), all with secondary and tertiary pulmonary tuberculosis, have been referred to Group 10.* These are of course the most interesting cases, as they should most likely be capable of transmitting the infection from man to man and from man to animals. That this is not only theoretically possible, but actually happened, has already been pointed out (see p. 110). Thus Case 8, who had a bovine primary complex in the left lung-hilar region and erythema nodosum (Figs. 6—7), was infected by Case 49, who had cavernous phthisis (Fig. 19). Case 62, who was affected with bilateral cavernous phthisis (Fig. 32), can almost certainly be said to have infected a previously tuberculous-free herd on a farm, where she had milked only 3 weeks before the detection of the extensive, highly infectious, pulmonary changes. But these cases are also of interest, since they show that bovine pulmonary tuberculosis in man is by no means rare in the Province of Skåne and that it is also very malignant.

Of the 28 cases belonging to this group 11 were males and 17 females. The age distribution of the cases is given in the following table.

As seen from the table, only one child, a girl aged 12, occurred among the cases. The others were adults, most of them belonging to the age group 20—26 years. A few cases, however, were of a still higher age. It is quite worthy of note that in 2 males the disease was first diagnosed at the age of 68 (Cases 40 and 67, Figs. 11 and 37). In the former of these two cases the disease had only a relatively slight extension at the time of diagnosis. A very serious diabetes present at the same time, however, caused the patient's

Table 8.

*Age distribution of the cases with secondary and tertiary pulmonary tuberculosis.*

Ages	M	F	Total
12	0	1	1
16—19	3	3	6
20—26	3	7	10
30—38	0	4	4
40—47	3	1	4
52	0	1	1
68	2	0	2
	11	17	28

death already after 6 months. In the latter case, on the other hand, the pulmonary changes were very extensive when the affection was diagnosed. Symptoms of the disease had been present for the past one or two years.

The source of infection was found in only 2 of the 28 cases belonging to this group, probably because in some cases a long time had elapsed since the primary infection was acquired. For instance, Case 46 had serofula 5 years before the development of the pulmonary tuberculosis. At least an equally long time must have elapsed between the primary infection and the onset of the tuberculous changes. In Case 49 there was an interval of 4 years between the erythema nodosum and the pulmonary tuberculosis. In Case 51 the radiograms revealed the presence of calcium deposits in the hilum and in one of the lungs. Provided that these residues were also of bovine origin, the interval between the primary infection and the pulmonary tuberculosis in this case must have been rather long. This is also true of Cases 52, 53 and 55, radiological evidence of an old tuberculosis of the abdominal lymph nodes being found, and of Case 62, which showed signs of an earlier tuberculosis of the cervical and axillary lymph nodes. In the majority of the cases, however, no evidence was found, from which it was possible to come to any definite conclusion as to when the bovine infection occurred.

In the 2 cases in which the source of infection was discovered the facts are as follows: Case 54 had milked and consumed raw milk from a herd, from which a cow had been slaughtered 3 years previously owing to its being affected with tuberculosis. Tuberculous disease had also occurred among the pigs on this farm. Case 56 was a milkmaid employed at a farm, where several cases of bovine tuberculosis in man had been discovered. The veterinary inspection of the cattle on this farm detected no less than 13 cows with open pulmonary tuberculosis, all of which were ordered to be slaughtered.

As in regard to the source of infection, the pathway by which the bovine bacilli had entered the body could be determined in only a few of the cases belonging to Group 10. In Cases 52, 53, 55 and 67, however, infection took place in all probability by way of the intestinal tract, an old tuberculosis of the abdominal lymph nodes being discovered. On the other hand, an inhalation infection may have taken place in Cases 47 and 51, calcareous changes being found in the lung and hilar regions, but not in the abdomen. In the other cases no changes were found in the abdomen, tonsils, lungs or hilar regions, by means of which the discovery of the pathway of infection is facilitated.

The symptoms in bovine secondary and tertiary pulmonary tuberculosis agreed in every respect with those in the corresponding affection due to human bacilli. Two of the cases (Cases 43 and 48) felt quite well at the time of diagnosis. The rate of sedimentation, however, was increased, 26 and 25 mm respectively. The changes in these cases were of a moderate extent. Bovine tubercle bacilli, however, were found in the sputum or in the gastric lavage. Case 46 had no pulmonary symptoms either, but this patient was troubled all the more with pains in the right ankle-joint due to tuberculous disease. The general physical examination on admission to hospital, however, revealed also rather small pulmonary changes (Fig. 16). The rate of sedimentation was greatly increased, 47 mm, and bovine tubercle bacilli were found in the gastric lavage. In most of the other cases the patients complained of cough, expectoration, loss of appetite, wasting, fever and fatigue. Stitch in the chest, dyspnoea, hoarseness and night sweats were also occasional symptoms. Haemoptysis occurred in 3 of the cases.

As a rule the rate of sedimentation was greatly increased; in 2 cases, Cases 60 and 66, it was even as high as  $> 120$ . At the time of diagnosis bovine tubercle bacilli usually occurred abundantly in the sputum.

The general appearance and character of the pulmonary changes will be clearly seen from Table 7 and numerous pictures showing *the condition at the time of diagnosis*. Nearly all the cases belonging to Group 10 are represented by pictures. In 8 of the cases the changes were at first in the left lung, in 8 cases in the right lung and in the remaining 12 cases they were bilateral. They varied, however, greatly in extent, being rather slight in 13 cases, fairly extensive in 9 cases and very extensive in 6 cases.

Of more importance than the extent of the lesions, however, are the nature of the changes and the occurrence of cavities. The malignancy of the changes already at the time of diagnosis can be seen from the pictures. *Thus not less than 19 of the 28 cases were exudative* (Figs. 13, 14, 17, 20, 21, 23—29, 31—36), *2 of which had even extensive pneumonic changes* (Figs. 21 and 23). *Cavity formation occurred already at the time of diagnosis in 20 of the cases* (Figs. 11, 13, 17, 19, 20, 24—37). The appearance of the radiograms was at times strikingly similar. Compare, for instance, the appearance of the changes in Figs. 24—27 and 34, all of which show a rather extensive, cloudy, more or less confluent mottling and the simultaneous occurrence of a cavity. Figs. 13, 17, 28 and 29 also present a very uniform appearance. In these cases the changes are seen as a rather small, cloudy density with a cavity in the centre.

Considering that the bovine pulmonary tuberculosis already at the time of diagnosis was so predominantly exudative and so frequently cavernous, there cannot be any doubt as to its malignancy. The subsequent development of the changes proved the correctness of this view. Of the 28 cases only 12<sup>1</sup> are now alive, the others died as a rule in the first or second year after the detection of the disease, in spite of all therapy. Five of these cases came to necropsy. Of the 12 surviving cases one is in a hopeless

<sup>1</sup> At the time of printing 2 more cases, Cases 44 and 45, have died from their tuberculous disease.

condition, but the others are doing rather well. The period of observation, however, is too short to permit me to say that they have passed the danger line. The majority of them are still undergoing pneumothorax treatment. *Thus it cannot be said that the present investigation has shown that bovine secondary and tertiary pulmonary tuberculosis in man is more benign than that due to human infection. In a very large number of the cases the changes proved themselves from the very beginning to be malignant and in their subsequent development frequently showed a rapidly progressive tendency in defiance of all therapy. Consequently bovine pulmonary tuberculosis in man is a severe affection with a very serious prognosis.*

Among the 67 cases there were altogether no less than 42 with primary, secondary or tertiary pulmonary changes. The latter then include all cases belonging to groups 2 and 10 (Table 6, p. 128). No pulmonary changes, it is true, could be radiologically shown in two of these cases, Cases 2 and 3, but the occurrence of tubercle bacilli in the sputum and in the gastric lavage suggests rather strongly the presence of a pulmonary lesion in addition to the hilar adenitis associated with the primary lesion. Cases 11 and 19, where the disease spread haematogenously to the lungs, and Case 29, in which pulmonary tuberculosis occurred at the same time as bone tuberculosis, have also been counted among these 42 cases. *A little more than 3 per cent of the cases of pulmonary tuberculosis in man typed were found to be of bovine origin. If a further 11 cases (Table 6, p. 128) found while the results of the investigation were being collocated are added to the 42 cases of pulmonary tuberculosis, thus altogether 53 cases of bovine primary, secondary and tertiary pulmonary tuberculosis have been shown in Skåne.*

### C. The epidemiology and clinical feature of bovine tuberculosis in man.

In the preceding analysis of the material I have several times touched on questions of great importance not only for our understanding of bovine tuberculosis in man but also for an effective campaign against this disease. In the following pages I shall

try to consider them in a somewhat wider relation. The questions I refer to are the following:

a) How does bovine tuberculous infection take place, and where in the human body does it produce its first changes (primary tuberculous)?

b) When and where is man exposed to the greatest risk of bovine primary infection?

c) What is the clinical picture of bovine primary tuberculosis in man?

d) How long is the interval between a bovine primary tuberculosis and the appearance of secondary and tertiary tuberculous changes?

e) What is the clinical picture of secondary and tertiary tuberculosis (of bovine origin) in man?

f) How is bovine tuberculosis diagnosed?

*a) How does bovine tuberculous infection take place, and where in the human body does it produce its first changes (primary tuberculosis)?*

That bovine tubercle bacilli are as a rule introduced into the human body along with milk or meat from tuberculous cattle is a fact acknowledged by all investigators in this field. The primary changes are therefore found most frequently in the abdomen (tuberculosis of the mesenteric lymph nodes) or in the cervical glands (the tonsils or associated cervical lymph nodes). From these foci the tuberculosis may subsequently spread haematogenously to different parts of the body and give rise to tuberculosis of the skin, bones, lymph nodes, urogenital organs, lungs, etc. Children are very frequently exposed to the risk of such an infection, chiefly on account of the large quantities of milk ingested. But even adults are exposed to the danger of getting an infection, especially if they are employed on farms where there are tuberculous cattle. The supply of milk is often included in their wages, and they therefore consume raw milk to a greater extent than other groups of the population. The danger involved in ingesting such milk is obvious,



and is defined by GRIFFITH (40) as follows: »There is little doubt that the greater part of human tuberculosis of bovine origin is due to infection conveyed in milk and milk products from tuberculous cows».

The possibility of an *aerogenous infection of human beings by bovine tubercle bacilli* was not brought into discussion until recent years. The problem began to arouse special interest when it was found that bovine tubercle bacilli may also produce pulmonary tuberculosis in man, a thing that was doubted not so many years ago. Whether pulmonary changes more frequently occur as the result of a metastasis from earlier intestinal foci or following an inhalation of bovine tubercle bacilli is still an open question however. That an inhalation tuberculosis can actually occur is obvious. In coughing, cows affected with pulmonary tuberculosis spread tubercle bacilli about them in the same manner as the human consumptive. The bacilli may be inhaled either immediately or later, when they are whirled about along with the dust in the stalls. The danger of infection by inhalation must therefore be exceedingly great for those persons employed in milking and tending cows, and whose dwelling-places are occasionally adjoining the byre. Since the question as to the frequency of such an inhalation tuberculosis is of great importance, not least for the future campaign against tuberculosis, it is necessary for me to give a brief account of the opinions of other investigators.

In one of his numerous, exceedingly valuable investigations published in 1930 GRIFFITH (39) wrote: »These observations suggest that 'bovine' phthisis pulmonalis may occur only in those persons, who are infected by the alimentary route and may never be transmitted as such from one person to another». In 1937 the same author (42) defines his view as follows: »One may conclude therefore that in Great Britain ulcerative pulmonary tuberculosis due to bacilli of the bovine type is in a large proportion of the cases the final phase of an infection acquired in childhood or adolescence or even in adult life through the consumption of infected milk». In this connexion GRIFFITH calls attention to the fact that in recent years cases of tuberculosis in children, mainly Scottish, had been found, »in which the anatomical evidence at autopsy was in favour of the respiratory tract as the portal of entry of the bacilli». Thus

the changes consisted of »enlarged and extensively caseous tracheo-bronchial glands with or without a primary focus in the lungs». The mesenterial lymph nodes, on the other hand, showed »no lesions whatever, or only miliary focus». GRIFFITH, it is true, does not dispute the possibility of some of these children having been infected through the inspired air, but he points out at the same time that »no connection has been traced between such a case and a case of bovine pulmonary tuberculosis and this is essential before air-borne infection can be finally accepted. For there are alternative explanations, namely, insufflation of infected milk or infection of the lung directly through the lymph and blood-streams from the alimentary canal».

In 1931, however, BRUNO LANGE (60) advocated the possibility of bovine infection taking place by the aerogenous route. In his opinion, bovine pulmonary tuberculosis in adults arises partly from an old tuberculous lesion caused by an infection in younger days through the intestinal tract, partly by aerogenous infection, »which is probably acquired not so infrequently at a later age». He believes (61) that especially agricultural workers, who come more into contact with tuberculous cattle than others, are exposed to the risk of bovine infection. BLACKLOCK (11) has described three cases of bovine primary thoracic infections. In two of these, one a child of 9 months, and the other aged 2 years and 3 months, no primary foci were found in the lungs, though the tracheo-bronchial glands were fairly extensively diseased. In the remaining case, that of a child aged 18 months, the most extensive tuberculous disease was found in the thoracic paratracheal glands.

Recently K. A. JENSEN in particular has called attention to the importance of bovine infection by the aerogenous route. In a work (53) published in 1940 in collaboration with LESTER and TOLDERLUND some very interesting points of view are put forward, which according to these authors »might indicate that also inhalation infection plays a rôle in the transmission of the bovine infection». Thus, it is pointed out that the large number of cases of bovine pulmonary tuberculosis in adult country people might indicate that these country people are exposed to a direct inhalation from the cattle besides the milk infection. In these cases the affection frequently ran a rapid and serious course, which, according to the

authors, does not seem reasonable to attribute to an alimentary infection. The demonstration of 15 cases of primary conjunctival tuberculosis caused by the bovine type — all adult country people in contact with cattle (milking) — also indicate, according to these authors, the possibility of a bovine inhalation tuberculosis. »When this can take place by getting dust or drops of tubercle bacilli-containing milk in the eyes, there can hardly be any doubt that they are liable to inhalation infection too». One of the cases observed by JENSEN (52), »in which it was practicable with great certainty to state that infection with the bovine type had been transmitted from man to man», argues also in the same direction. JENSEN, LESTER and TOLDERLUND sum up their view of this problem as follows: »Taking all these findings into consideration, one arrives at the result that the bovine type is able to infect man not only through the digestive tract but also through the respiratory passages, and that a stable in which tuberculous cows are kept throughout the winter undoubtedly involves the same risk of infection as does, for instance, a tuberculosis sanatorium».

At the same time as the above-mentioned investigation very strongly emphasizes the importance of bovine infection by the aerogenous route, it also calls attention to two more pathways by which bovine infection can take place, viz. *by dust and dirt and by transmission from one person affected with bovine pulmonary tuberculosis to another*. Judging from the investigations of K. A. JENSEN and O. BLEGVAD, infection by the former route seems to be by no means rare. The latter mode of infection is probably not uncommon either, although the evidence so far advanced is not conclusive. The detection of several cases of tuberculosis in a consumptive's family is not sufficient proof of the transmission of bovine infection from one human being to another. Proof must also be obtained that they are caused by *bovine* tubercle bacilli. A further examination will not infrequently show that the tuberculous affection of the other members of the family is of *human* origin (see Cases 42 and 45), and that therefore the case of bovine tuberculosis simply occurs in a family probably less resistant to tuberculous infections on the whole. I have already in a previous chapter advanced the view that the following conditions must be



3-bedroom together with two bacillary phthisics (patients A and B) with a marked degree of tuberculosis. In the latter part of October the Pirquet test turned out negative, and then the patient was transferred to a tuberculosis-free room, and it was the intention to discharge her in a near future. The Pirquet test was repeated on 15/11 1932, and now it turned out positive. A few days later her temperature was subfebrile, and she began to feel ill. The temperature rose slowly but rather steadily, staying finally between 38° and 39° C. Roentgenography was repeated on 30/11, and now it showed a massive infiltration at the hilum. On 2/12 the patient had erythema nodosum. The sedimentation rate was then 27 mm. On 23/12 gastric lavage was sent to this laboratory for examination for tubercle bacilli and cultures herefrom showed a typical bovine strain that was virulent for rabbit on subcutaneous inoculation with 10 mg. of the culture. The patient was discharged from the sanatorium at the request of her parents, and it has not been possible to make her return for re-examination.

Now the strains of tubercle bacilli cultivated from the two patients, A and B, who stayed in the same sickroom, were type-determined with this result: Patient A. Sputum, received on 29/3 and 1/6 33, gave growth of human tubercle in pure culture. Patient B. Sputum, received on 24/4 33, gave growth of bovine tubercle bacilli in pure culture that proved highly virulent for rabbit.

In my opinion, the above cases of MUNRO and of JENSEN furnish indubitable proof that bovine infection can really be transmitted from one human being to another. To these cases can now be added the following two cases observed by me. In one of these the source of infection was a woman, aged 24, with cavernous phthisis and abundant bovine tubercle bacilli in the sputum (Case 49, Fig. 19). Her infectiosity can be gathered from the fact that both her husband and a 7-year-old sister got tuberculosis. Even 2 previously non-tuberculous cows belonging to the small farm became tuberculin reactive. The husband developed a very severe exudative pleurisy, which necessitated a long period of hospital care. Examinations, however, failed to reveal tubercle bacilli and therefore the bovine origin of the changes could not be proved. On the other hand, the sister (Case 8, Figs. 6—7), had, in addition to erythema nodosum, a primary complex in the left lung and hilar region. Bovine tubercle bacilli were isolated from the gastric lavage. The possibility of a fresh infection from the cattle belonging to the farm could be excluded. The particulars of this case are given in pages 28—30.

The other case was discovered after the conclusion of the investigation, while the material was being worked up for publication, and is therefore not included in the Case Histories. The source of infection was a foundry worker, aged 22, living just outside the town of Ystad. In 1937 and 1938 he had been treated at Lund Hospital for tuberculosis of the cervical lymph nodes. At that time the lungs were radiographically normal, but examination in April 1940 revealed an extensive left-sided pulmonary tuberculosis. At the apex there were two cavities the size of walnuts (Fig. 40). *Tubercle bacilli were found in very large numbers in the sputum*, which when typed were found to be bovine. The patient was at once admitted to sanatorium, and after thoracoplasty is in a rather good condition.

At about the same time as the detection of the father's bovine pulmonary tuberculosis, parenchymal changes at the apex and base of the right lung and a considerable enlargement of the mediastinal lymph nodes (primary complex) were shown in a 3-year-old son (Fig. 41). As an expression of the haematogenous spread of the tuberculous affection there also appeared *spina ventosa and multiple abscesses* under the skin, which *were* subsequently found to contain bovine tubercle bacilli. The child's condition gradually improved.

Further examination of the family revealed the presence of a fresh left-sided hilar adenitis in a brother, aged 3, and small pulmonary changes in the father of the patient. Examination, however, failed to reveal tubercle bacilli in these two cases. The milk consumed was pasteurised, therefore the infection was evidently transmitted from person to person within the family.

From the above views the following conclusions may be drawn: Bovine tuberculosis in man is most commonly caused by the ingestion of milk and meat from tuberculous cows. The first changes (primary tuberculosis) therefore consist as a rule of tuberculosis of the mesenteric or cervical lymph nodes (tonsillar tuberculosis). Further, bovine infection may be acquired by the impregnation of dirt and dust (cutaneous tuberculosis, conjunctival tuberculosis and tuberculosis of cervical lymph glands). But bovine tuberculosis in man may occur also by the aerogenous route, the changes in that case presenting as a rule the picture of a hilar adenitis or a

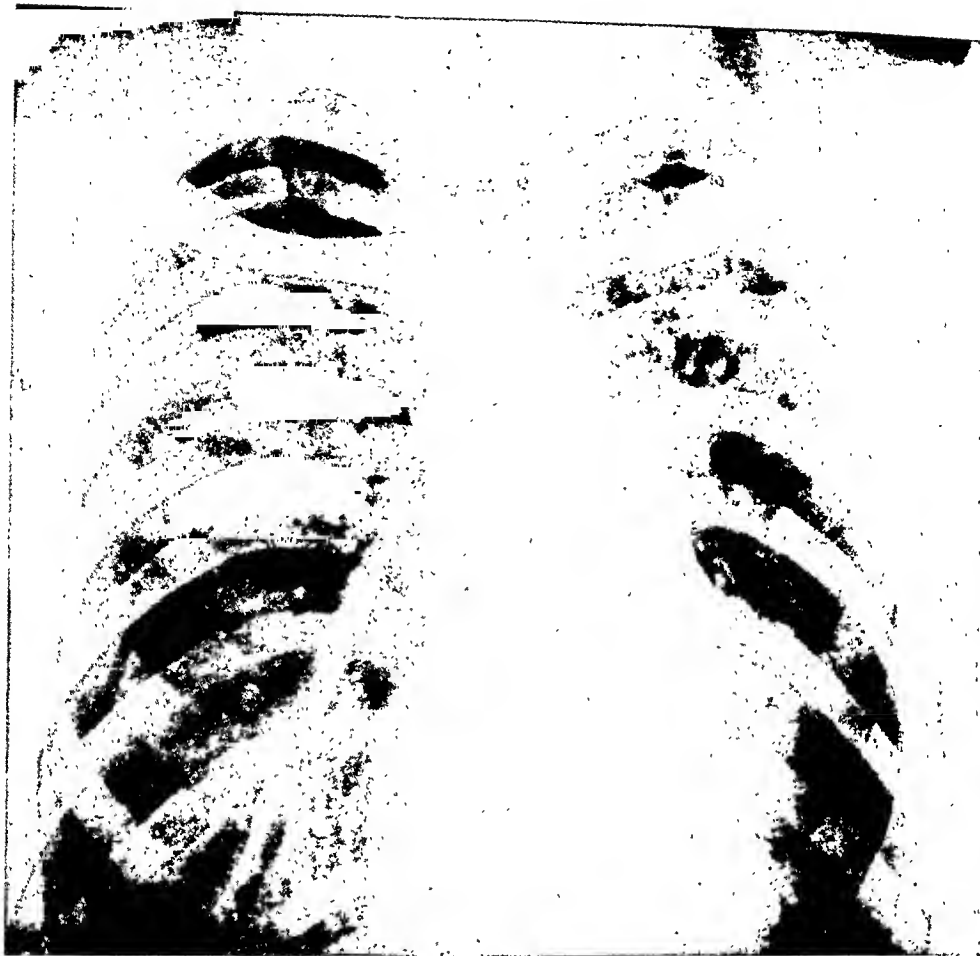


Fig. 40.

A man, aged 22 (foundry worker), with left-sided cavernous phthisis of bovine origin. The film shows tuberculous changes in the greater part of the left lung in addition to two cavities the size of walnuts at the left apex. *Bovine tubercle bacilli* were found in very large numbers in the sputum. The patient's condition has improved as the result of thoracoplasty.

The patient transmitted the disease to the case shown in Fig. 41.

primary complex. Evidence in support of air-borne infection is afforded in the first place by the 4 cases mentioned above, where an aerogenous transmission of bovine tuberculosis from man to man undoubtedly occurred. Further evidence of this pathway of infection is furnished by a number of observations of cases of hilar adenitis, with or without changes of the lung, agreeing completely in appearance with that seen in human primary tuber-

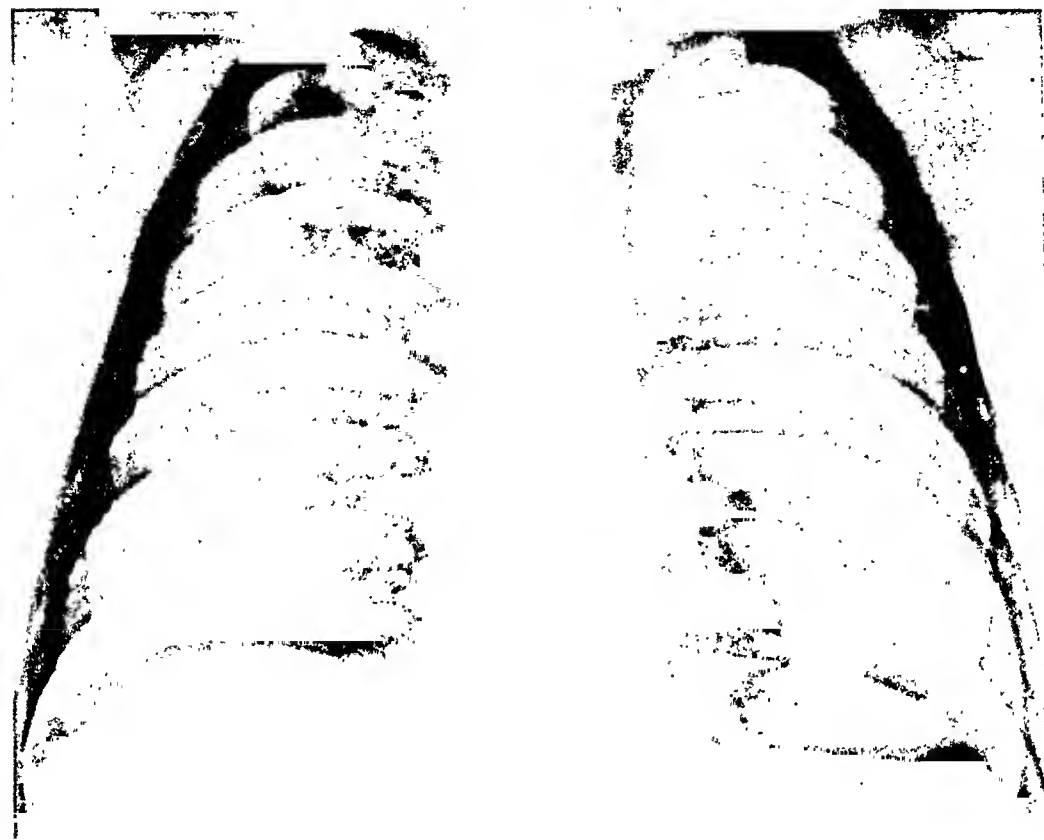


Fig. 41.

A boy of 3 years, a son of the patient recorded on p. 158 and in Fig. 40. The radiogram shows tuberculous changes in the right lung and in the mediastinum (primary complex). The patient, whose condition gradually improved, had at the same time *spina ventosa* and multiple *cutaneous abscesses*, from which *bovine tubercle bacilli* were cultivated. The source of infection was the father.

culosis (Cases 2—10). On the other hand, it is not yet certain whether the relatively common occurrence of bovine pulmonary tuberculosis among those milking or tending cows, etc. is *generally* due to repeated inhalations of tubercle bacilli. Such persons also consume large quantities of milk from the farms, consequently at least some of these cases were very probably caused by metastasis from intestinal foci.

In order to obtain the greatest possible clarity as to the route of infection it is essential, in my opinion, that bovine tuberculosis in man is studied as uniformly as possible. The problem concerning



the paths by which infection enters is important, for if bovine tuberculosis is relatively frequently acquired by the aerogenous route new and adequate measures must be taken to prevent such infections. Our present measures are mainly devoted to the prevention of alimentary tuberculosis.

1) In *fresh* infection careful search must be made for the site of the *first* tuberculous changes. In such cases it is generally easy to find the source of infection and thus determine the interval of time within which infection may have taken place. The time of infection may also be estimated approximately if the patient develops erythema nodosum, which evidently appears in a relatively large number of cases in association with the primary infection, at any rate in Sweden (v. Cases 2—5, 8, 9 and 15).

2) If bovine tuberculosis has already developed, valuable information as to a previous tuberculous infection may be obtained from the patient's past history. Radiographic examination is necessary not only of the lungs but also of the abdomen. Research into the existence of residues of tuberculosis (calcification, fibrosis, etc.) must be made. Tonsils and cervical lymph nodes must also be carefully examined. In the event of autopsy it is of the greatest importance not only to study the extent of the tuberculous disease but also methodically to look for the site of the primary lesion.

As far as possible the 67 cases included in the present classification were investigated in the manner described above. For the sake of perspicuity the observations made have been presented in Table 9. Further particulars of the different cases will be found in the Case Histories on pages 19—101, and in the analysis of the cases on pages 102—152. As seen from the table the pathway of infection was intestinal in 12 cases, tonsillar in 3 certain cases and in 1 uncertain case, aerogenous in 14 certain and 2 uncertain cases, while in 35 cases the route of infection could not be determined. It is noteworthy that 23 of the last-mentioned cases had pulmonary tuberculosis. It is quite possible that some of them were infected by the aerogenous route. In 2 cases *primary intestinal infection* gave rise to miliary tuberculosis and tuberculous meningitis (Cases 11 and 12), in 1 case to tuberculous meningitis (Case 13), in 2 cases to tuberculous peritonitis (Cases 16 and 17), in 1 case to bone tuberculosis with an abscess (Case 27), in 2 cases to renal tuberculosis

Table 9.  
Route of infection

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
1	4	No changes. T. B. in gastric lavage.				+
2	5	<i>Erythema nodosum and pulmonary and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection (Fig. 1). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T.B. in sputum and gastric lavage.			+	
3	7	<i>Erythema nodosum and hilar adenitis</i> due to a <i>fresh</i> tuberculous infection from a known source of infection (Fig. 2). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in gastric lavage.			+	
4	10	<i>Erythema nodosum and hilar adenitis</i> due to a <i>fresh</i> tuberculous infection from a known source of infection. No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in sputum and gastric lavage.			+	
5	16	<i>Erythema nodosum, lung and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection. No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in gastric lavage.			+	
6	29	<i>Lung and hilar changes</i> (Fig. 3). Source of infection unknown. No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Abdomen was not radiographed. T. B. in sputum and gastric lavage.			?	
7	14	<i>Pulmonary and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection (Figs. 4—5). When patient became ill, the tuberculin reaction was negative, but soon became strongly positive. No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in sputum and gastric lavage. <i>Autopsy</i> 1 year later confirmed assumption of location of primary lesion in the lungs.			+	

## Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	un-certain
8	7	<i>Erythema nodosum and pulmonary and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection (Figs. 6—7). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in gastric lavage.			+	
9	23	<i>Erythema nodosum and pulmonary and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection. No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax (abdomen not radiographed). T. B. in sputum			+	
10	30	<i>Pulmonary and hilar changes</i> due to a <i>fresh</i> tuberculous infection from a known source of infection (Figs. 8—9). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in pleural fluid and lung tissue. <i>Autopsy</i> , 13 months after primary infection, proved occurrence of inhalation tuberculosis.			+	
11	6	<i>Acute miliary tuberculosis</i> (Fig. 10) and <i>tuberculous meningitis</i> , secondary to bovine primary infection of abdomen. <i>Confirmed by autopsy</i> .	+			
12	15 mths	<i>Acute miliary tuberculosis and tuberculous meningitis</i> , secondary to primary tuberculosis of abdomen. <i>Confirmed by autopsy</i> .	+			
13	7 mths	<i>Tuberculous meningitis with preceding abdominal trouble</i> . No X-ray examination of abdomen and lungs. No autopsy, patient dying at home.	+			
14	23	<i>Exudative tuberculous pleurisy</i> . No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in pleural exudate. Patient did not like milk and had therefore not consumed any milk for more than 15 years. Source of infection unknown.			?	
15	41	<i>Exudative tuberculous pleurisy</i> . 17 months previously a <i>fresh</i> tuberculous infection with erythema nodosum, pulmonary and hilar changes and initial foci at apex of left lung.			+	

Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
16	16	<i>Tuberculous peritonitis</i> , secondary to primary bovine infection in abdomen from known source of infection. <i>Confirmed by autopsy.</i>	+			
17	10 mths	<i>Tuberculous peritonitis</i> , secondary to bovine primary abdominal tuberculosis. Source of infection found. <i>Confirmed by autopsy.</i>	+			
18	15 mths	<i>Tuberculosis of cervical lymph nodes</i> due to a <i>fresh</i> bovine tuberculous infection from a known source of infection. Lung and hilar regions normal. No calcified lymph nodes in thorax or abdomen. T. B. in gastric lavage.		?		
19	3	<i>Tuberculosis of cervical lymph nodes</i> , miliary dissemination causing death. <i>Autopsy</i> confirmed primary changes in cervical lymph nodes.		+		
20	5	<i>Tuberculosis of tonsils and cervical lymph nodes</i> . Normal lungs. No X-ray examination of abdomen. T. B. in tonsillar tissue.		+		
21	21	<i>Tuberculosis of cervical lymph nodes</i> . Normal lungs. No X-ray examination of abdomen. T. B. in cervical lymph nodes.				+
22	17	<i>Tuberculosis of cervical lymph nodes</i> . No X-ray examination of lungs or abdomen. T. B. in cervical lymph nodes.				+
23	7	<i>Tuberculosis of tonsils and cervical lymph nodes</i> . No X-ray examination of lungs or abdomen. T. B. in tonsillar tissue.		+		
24	4	<i>Phlyctena, tuberculosis of cervical lymph nodes</i> (containing calcium deposits), <i>hilar adenitis with transient perihilar infiltration</i> . No calcified lymph nodes in hilum. No X-ray examination of abdomen. T. B. in gastric lavage.				+
25	5	<i>Bone tuberculosis with abscess</i> . Normal lungs. No calcified lymph nodes in thorax. No X-ray examination of abdomen. No abdominal trouble. T. B. in abscess.				+
26	20	<i>Bone tuberculosis with abscess</i> . No X-ray examination of lungs and abdomen. T. B. in abscess				+

## Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
27	6	<i>Bone tuberculosis with abscess.</i> Considerable abdominal trouble some time before appearance of bone changes. No X-ray examination of lungs and abdomen. T. B. in abscess.	+			
28	62	<i>Bone tuberculosis.</i> Calcified primary complex in right lung and hilar region. X-ray examination of abdomen showed no calcified lymph nodes. T. B. in abscess.			+	
29	29	<i>Bone and pulmonary tuberculosis.</i> No tuberculosis of cervical lymph nodes. No calcified nodes in thorax or abdomen. Pulmonary changes certainly not primary. T. B. found only in punctate from knee-joint.				+
30	29	<i>Urogenital tuberculosis.</i> No X-ray examination of lungs or abdomen. T. B. in urine.				+
31	23	<i>Renal tuberculosis and bursitis, tbc. tuberositis, tibiae.</i> Normal lungs. No calcified lymph nodes in thorax. No X-ray examination of abdomen. T. B. in urine.				+
32	28	<i>Renal tuberculosis.</i> No X-ray examination of lungs or abdomen. T. B. in urine.				+
33	28	<i>Renal tuberculosis.</i> Normal lungs. No calcified lymph nodes in thorax. No X-ray examination of abdomen. T. B. in urine.				+
34	25	<i>Renal tuberculosis.</i> Calcified primary complex in left lung and hilar region. No evidence of calcified lymph nodes in abdomen. T. B. in urine.			+	
35	34	<i>Renal tuberculosis.</i> Normal lungs. Numerous calcified lymph nodes in abdomen but none in thorax. Abdominal trouble for a long time previously. T. B. in pyonephrotic sac.	+			
36	34	<i>Renal tuberculosis.</i> Normal lungs. No calcified lymph nodes in thorax, but found in abdomen. T. B. in urine.	+			
37	25	<i>Renal tuberculosis.</i> Normal lungs. No calcified lymph nodes in thorax. No X-ray examination of abdomen. T. B. in urine.				+

Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
38	32	<i>Renal tuberculosis.</i> Left-sided pleurisy and large calcium deposits in left lung as far back as 1916. Later right-sided epididymitis and tuberculosis of right seminal vesicle (1934), left-sided epididymitis and bilateral renal tuberculosis (1935), right-sided pleurisy (1937). Bovine T. B. in urine in 1937. Cervical lymph nodes normal. No calcified lymph nodes in abdomen.			+	
39	18	<i>Renal and pulmonary tuberculosis</i> due to a relatively fresh tuberculous infection (erythema nodosum about 2 years previously). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen. T. B. in urine.				+
40	68	<i>Pulmonary tuberculosis</i> (Fig. 11). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen not taken.				+
41	40	<i>Pulmonary tuberculosis</i> (Fig. 12). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen not taken.				+
42	23	<i>Pulmonary tuberculosis</i> (Fig. 13). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen.				+
43	16	<i>Pulmonary tuberculosis.</i> No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen not taken.				+
44	26	<i>Pulmonary tuberculosis</i> (Fig. 14). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen was not taken.				+
45	40	<i>Bilateral pleurisy, one year later bilateral pulmonary tuberculosis</i> , both of bovine origin (Fig. 15). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax or abdomen.				+
46	18	<i>Pulmonary and bone tuberculosis (scrofula</i> 5 years previously) (Fig. 16). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen was not taken.				+

Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
47	17	<i>Pulmonary tuberculosis</i> (Fig. 17). No tuberculosis of cervical lymph nodes. Calcification in left hilar region, indicating earlier hilar gland tuberculosis. No calcified lymph nodes in abdomen.			+	
48	35	<i>Pulmonary tuberculosis (exudative pleurisy 7 years previously)</i> (Fig. 18). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen was not taken.				+
49	24	<i>Pulmonary tuberculosis (erythema nodosum 4 years previously)</i> (Fig. 19). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen was not taken.				+
50	47	<i>Pulmonary tuberculosis</i> (Fig. 20). No tuberculosis of cervical lymph nodes. No calcified lymph nodes in thorax. Radiogram of abdomen was not taken.				+
51	12	<i>Pulmonary tuberculosis</i> (Fig. 21). No tuberculosis of cervical lymph nodes. Large calcium deposits in both hilar regions. Small calcium deposits at apex of right lung. Abdominal radiogram showed no calcified lymph nodes.			+	
52	18	<i>Pulmonary and cervical gland tuberculosis</i> (Figs. 22—23). Tuberculous nodes on neck. Calcified cervical lymph nodes (extending over right supraclavicular region) and also calcified nodes in right hilum. Very extensive calcification of lymph nodes in abdomen. <i>Autopsy</i> confirmed location of primary infection in abdomen.	+			
53	30	<i>Pulmonary and cervical gland tuberculosis</i> . Calcified lymph nodes in abdomen, but none in thorax.	+			
54	16	<i>Pulmonary tuberculosis</i> (Fig. 24). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes in thorax or abdomen.				+
55	21	<i>Pulmonary tuberculosis</i> (Fig. 25). No tuberculosis of cervical lymph nodes. Numerous	+			

Continued

No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
		calcified lymph nodes in abdomen, but none in thorax. <i>Autopsy</i> confirmed site of primary infection in abdomen.				
56	25	<i>Pulmonary tuberculosis</i> (Fig. 26). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes in thorax or abdomen. Source of infection found.				+
57	42	<i>Pulmonary tuberculosis</i> (Fig. 27). No calcified lymph nodes in thorax. No radiogram of abdomen made. <i>Autopsy</i> did not reveal any evidence of tuberculosis of mesenteric or intestinal lymph nodes.				+
58	22	<i>Pulmonary tuberculosis</i> (Fig. 28). No tuberculosis of cervical lymph nodes. Radiogram of abdomen was not taken. No calcified lymph nodes in thorax.				+
59	38	<i>Pulmonary tuberculosis</i> (Fig. 29). No tuberculosis of cervical lymph nodes. Radiogram of abdomen was not taken. No calcified lymph nodes in thorax.				+
60	52	<i>Pulmonary tuberculosis</i> (27 years previously exudative pleurisy) (Fig. 30). No tuberculosis of cervical lymph nodes. Abdominal radiogram was not taken. No calcified lymph nodes in thorax.				+
61	20	<i>Pulmonary tuberculosis</i> (Fig. 31). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes found in thorax or abdomen.				+
62	24	<i>Pulmonary and laryngeal tuberculosis</i> (Fig. 32). Large numbers of calcified lymph nodes in both axillae and on neck, but none in hilar regions. No radiographic examination of abdomen performed.				+
63	21	<i>Pulmonary tuberculosis</i> (Fig. 33). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes in thorax. Radiographic examination of abdomen was not performed.				+
64	25	<i>Pulmonary tuberculosis</i> (Fig. 34). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes found in thorax or abdomen.				+



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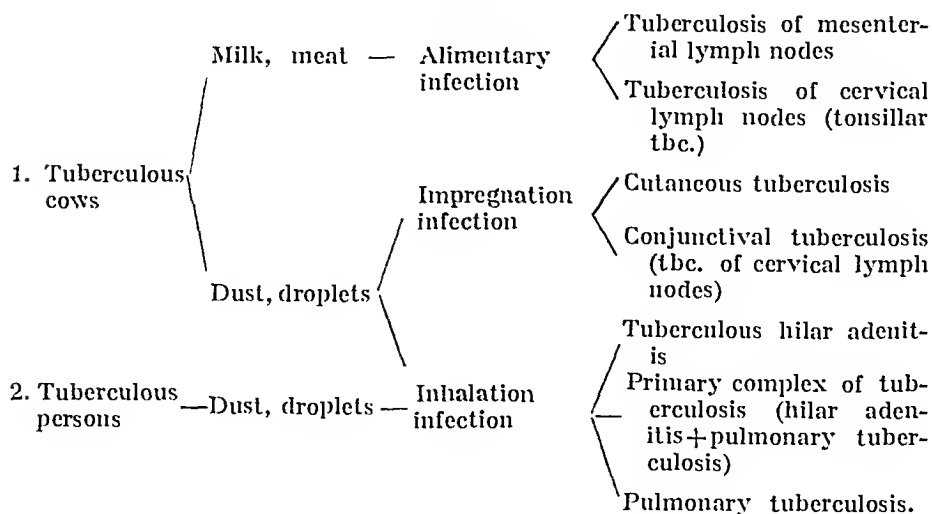
No. of case	Age	Main clinical features	Site of primary lesion			
			in abdomen	in tonsils or cerv. lymph n.	in lungs	uncertain
65	31	<i>Pulmonary tuberculosis</i> (Fig. 35). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes found in thorax or abdomen.				+
66	19	<i>Pulmonary tuberculosis</i> (Fig. 36). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes found in thorax or abdomen.				+
67	68	<i>Pulmonary tuberculosis</i> (Fig. 37). No tuberculosis of cervical lymph nodes, and no calcified lymph nodes in thorax. Radiogram of abdomen was not taken. <i>Autopsy</i> revealed, however, the presence of old, calcified mesenterial lymph nodes.	+			

(Cases 35 and 36) and in 4 cases to pulmonary tuberculosis (Cases 52, 53, 55 and 67; Figs. 22, 23, 25, 37). *Tonsillar infection* was the cause of 3 cases of tuberculosis of the cervical lymph nodes (Cases 19, 20 and 23). To these should be added one uncertain case (Case 18), in which tuberculosis of the cervical lymph nodes occurred as the result of a fresh tuberculous infection originating from a known source of infection. Since no changes could be demonstrated in the lungs (or hilar regions) and in the abdomen, but bovine tubercle bacilli were found in the stomach washing, the route of infection was probably by the tonsils. The bacilli were probably swallowed from the tuberculous lesions in the tonsils but no proof is available as excision was not performed. *Aerogenous primary infection* brought about a primary complex in one of the lungs and the corresponding hilar region in 2 cases (Cases 7 and 10, Figs. 4, 5, 8, 9), a primary complex and erythema nodosum in 4 cases (Cases 2, 5, 8 and 9, Figs. 1, 6, 7), hilar adenitis and erythema nodosum in 2 cases (Cases 3 and 4; Fig. 2), a primary complex, erythema nodosum and incipient pulmonary tuberculosis, and 17 months later exudative pleurisy in 1 case (Case 15), a bone tuberculosis in 1 case (Case 28), a renal tuberculosis in 2 cases (Cases 34 and 38), and, finally, pulmonary tuberculosis in 2 cases (Cases 47 and 51). It should be noted that in the majority of these cases the source of infection was discovered and that the connexion between the infection and the occurrence of the primary

lung and hilar changes was rather clearly elucidated. Some of the cases were children of the same family and became ill at about the same time. In 2 more cases the pathway of infection was most probably aerogenous (Cases 6 and 14). Case 6 developed changes reminiscent of a primary complex in the lung and the corresponding hilar region (Fig. 3). Case 14, who had an exudative pleurisy, had milked and tended cows, but had not consumed any milk for more than 15 years.

*The present investigation thus indicates that bovine tuberculosis in man may occur not only by ingesting milk from tuberculous cows and by the impregnation of bacillus-carrying dust, but also by the inhalation of tubercle bacilli. The surprisingly large number of tuberculous cases due to aerogenous infection found in our investigation in fact goes to prove that this route of infection plays a much greater role than was formerly ascribed to it. Laboratory infection has also been observed (Case 9). Bovine infection can also be transmitted from man to man (p. 148 and 156—159) and from man to cattle (p. 148). No matter by what route the bovine tubercle bacilli enter the system the disease may spread haematogenously to other parts of the body and give rise to secondary and tertiary tuberculosis. Bovine primary tuberculous changes are met with not only in the mesenterial and cervical lymph nodes (tonsils, conjunctiva) but also in the lungs and in the lymph nodes of the hilum and of the mediastinum. The following schema (Table 10) may therefore be drawn to illustrate the sources of infection, pathways of infections and the location of the first changes, thereby answering the question asked:*

Table 10.



*b) When and where is man exposed to the greatest risk of a bovine primary infection?*

Under certain conditions an approximate idea of the time at which a primary bovine infection takes place may be obtained by studying the occurrence of bovine tuberculosis in man at different ages. If most of the cases of this disease are found among children it is obvious that the primary infection takes place as a rule during the first years of life. On the other hand, it is a more difficult matter to determine when the primary infection took place if the affection is found in adults — unless one has to do with primary tuberculous changes. If no guidance is obtained from the patient's past history, or if no radiological or other evidence of an earlier primary tuberculous infection can be found, it is simply impossible to determine whether the changes are the result of a fresh or of an old primary infection.

In 1928 B. MÖLLERS (77) published a list of all cases of bovine tuberculosis in man so far recorded and verified by isolating and typing the bacilli. The number of cases amounted to 258, of which 209 were children (134 between the ages 0—4 years, 75 between the ages 5—15 years). The remaining cases were adults. Since then other investigations have disclosed a very large number of new cases of bovine tuberculosis, particularly of the extrapulmonary type. In 1937 GERVOIS (31) gave the total number of cases at 1912, of which 402 were adults, the others children in the ages of 0—15 years. From these two classifications it can be gathered that the risk of acquiring a primary bovine infection is especially great in childhood, which is indeed quite natural, as children as a rule consume large quantities of milk regularly. GRIFFITH (43) wrote in 1938 that in England the incidence of bovine infections is highest in children under 5 years of age. In cervical gland cases, it exceeds 90 %, and in other forms ranges from 28 to 58 %. Also in Scotland the highest incidence of bovine infections is in children under 5 years of age. In primary abdominal tuberculosis the percentages for the two countries are about the same, namely 80 and 82 %. Thus primary abdominal tuberculosis is, as a rule, caused by bovine bacilli, but as pointed out on several occasions by A. PETTERSSON (86—88), this form of the disease may also be produced by

the human bacillus. In fact primary abdominal infections due to the human bacillus are more common than is generally supposed. In 1933, in a classification of 139 cases of primary intestinal tuberculosis, partly his own cases and partly cases recorded in the literature, PETTERSSON was able to show that 56.1 % were due to the bovine tubercle bacillus and 43.9 % to the human type. Of the bovine cases, 51 were found in the ages of 0—5 years, 21 in the ages of 6—15 years and only 6 above 15 years of age.

The risk of acquiring a bovine infection is greater in the country than in towns. JENSEN, LESTER and TOLDERLUND (53) wrote quite recently that in Denmark in the towns the bovine infection occurs especially in children under 15 years; in the rural population, on the other hand, where the bovine infection is particularly frequent, it occurs fairly often in adults. The cause of this is that while towns-people are infected only by ingesting milk, the country population is liable to direct contact infection from the cattle in addition to alimentary infection. This explanation seems to me to be very probable. People milking and tending cows, and others in constant contact with cattle, must inevitably run a greater risk of infection through direct contact than persons having other occupations. The same thing applies to the children of such families, owing to the fact that they often play or assist in the work in the cow-stalls. But it should also be borne in mind that these families certainly consume tuberclebacilli-containing milk more frequently and in larger quantities than persons belonging to other groups of the population. The danger of a primary bovine infection, on the other hand, is much less for the urban population supplied with only pasteurised or tuberculous-free milk. The urban population is therefore usually infected during a temporary stay in the country (holidays, etc.).

Thus bovine tuberculosis in man is essentially a rural problem. The correctness of this view is also evident from the present investigation. At the end of 1938 the population of the Province of Skåne amounted to 773,363 persons, 326,338 living in the towns and 447,025 in the country. In spite of the relatively high figure for the urban population only 14 cases of bovine tuberculosis were found among towns-people, several of whom were almost certainly primarily infected during an earlier stay in the country. The major-

rity of the tuberculous cases, 53 out of 67, were persons living in rural districts. But even in the country the risk of infection varies. Occupation plays an important role. Thus not less than 43 of the 67 cases had occupations involving an intimate contact with cattle (veterinarians, butchers, farmers, tenant-farmers, cowmen, farm-servants, farm-labourers, etc. and their wives or children).

The time at which the primary infection took place could be determined exactly in 9 cases (Group 2, Table 6), on account of the appearance of changes characteristic of primary tuberculosis. Five of these cases were children aged 5, 7, 7, 10 and 14 respectively. In the remaining 4 cases primary infection did not take place until adult age (16, 23, 29 and 30 years of age respectively). In cases 15, 39 and 49, too, the primary infection occurred in adults. Case 15 had erythema nodosum, tuberculous primary complex and incipient pulm. tbc at the age of 39, exudative pleurisy 2 years later, while Case 39 had erythema nodosum at the age of 16 and renal and pulmonary tuberculosis 2 years later. Case 49 had erythema nodosum at the age of 20 and cavernous phthisis 4 years later. *Primary bovine infection in adult age is obviously not rare.* The onset of the primary infection can also be estimated roughly when bovine tuberculosis of secondary or tertiary type is diagnosed in children. In Cases 11—13, 16—20, 23—25 and 27, altogether 12 cases, bovine tuberculosis occurred in children under 7 years of age. There is therefore no doubt that these children were primarily infected at a very early age. The same thing is true of Case 1, who gave a positive tuberculin reaction already at the age of 4 years and of Cases 47, 51 and 52, who were only 17, 12 and 18 years respectively and showed — in addition to pulmonary tuberculosis — calcified rests of an old tuberculosis either in the lungs and hilar regions or in the abdomen.

*To sum up, it may thus be said that primary infection generally takes place in childhood. In some cases, however, it does not occur until adult age. There is reason to believe that adult infection is even rather common. Country people are infected to a greater extent than the urban population. Persons whose occupations bring them into close contact with cattle — milkmaids, cattle-tenders, veterinarians, etc. — as well as their families, particularly the children, are exposed to the greatest risk of infection. Bovine tuberculosis in man is therefore essentially a rural problem.*

*c) What is the clinical picture of bovine primary tuberculosis in man?*

In earlier works on bovine tuberculosis in man relatively little interest was devoted to the clinical picture of primary tuberculosis. Further, in the description of the cases no differentiation was made generally between primary, secondary and tertiary changes, and as far as I have been able to find no reproductions illustrating the appearance of the different stages of pulmonary tuberculosis were furnished.

Medical literature is therefore not very rich in accounts of primary bovine infection. A certain amount of information can, however, be gathered from descriptions of bovine epidemics, where the source of infection was traced and the time at which the primary infection took place estimated as nearly as possible. A few such epidemics have been observed recently in different places in Sweden. As they supplement my own observations in certain respects I shall give a brief account of them below. As already mentioned, small familial epidemics were also observed by us in the Province of Skåne. In one of them 6 children of the same family were infected at the same time. All the children were ill for quite a long time. Three of these children had erythema nodosum and hilar adenitis, one had erythema nodosum, pulmonary tuberculosis and hilar adenitis (a primary complex). Bovine tubercle bacilli, however, were demonstrated in only 3 of them (Cases 2—4). The source of infection was tuberculous cows belonging to the farm. In another epidemic 4 children of the same family were taken ill. One of them had erythema nodosum, 2 had erythema nodosum with pulmonary tuberculosis and hilar adenitis (a primary complex), while the fourth had tuberculosis of the abdominal lymph nodes. Bovine tubercle bacilli were shown in one of the children (Case 5). The source of infection here, too, was found among the cows on the farm.

A more extensive epidemic of bovine tuberculosis is reported by TÖRNELL (126, 127). It took place in a small holiday camp for 13 children from the city of Gothenburg. On arrival at the camp the children were tuberculin negative, but after some time they became ill and gave a positive reaction to the test. Some of them had erythema nodosum, others developed intestinal trouble. No source of infection could be detected among the staff. A further investi-

gation, however, revealed that the children had been given milk from a cow affected with tuberculosis of the udder. This milk was found to contain bovine tubercle bacilli. — Another outbreak occurred at a factory in the neighbourhood of the town of Borås, where 13 girls had erythema nodosum. The cutaneous changes had been preceded by moderate throat trouble. Some of the patients later showed a protracted enlargement of the lymph nodes at the mandibular angles. The tuberculin reaction was positive and the rate of sedimentation increased. The radiogram of the lungs was in general normal. One of the girls, however, showed a moderate enlargement of the hilar glands, and another two small infiltrations in the lung. Later the last-mentioned patient developed exudative pleurisy. The source of infection could not be discovered in the factory, where the patients had been occupied in different halls. All had, however, consumed milk supplied from the same dairy. This milk was found to contain bovine tubercle bacilli. FOGSTRAND (26) has reported an extensive epidemic in the Province of Värmland, in which some 40 persons, chiefly children and young people, became ill at the same time with symptoms of tuberculosis of the cervical lymph nodes. At least half of them had erythema nodosum, several developed phlyctena and two had peritoneal tuberculosis. All the infected persons had consumed milk from a cow affected with tuberculosis of the udder. A radiological examination of the lungs was made in the majority of the cases, but no, or only slight, changes were discernible in the hilar lymph nodes. GARDELL (29) observed another epidemic in Värmland among working-class families at a paper mill. Not less than 44 persons were affected, 20 of whom had erythema nodosum alone, 10 tuberculosis of the cervical lymph nodes alone, 9 erythema nodosum and tuberculosis of the cervical lymph nodes, 1 erythema nodosum and phlyctena, 1 tuberculosis of the mesenteric nodes and phlyctena, 1 tuberculosis of the cervical and mesenteric lymph nodes and phlyctena, 1 tuberculous peritonitis and ileus, and 1 only fever. The source of infection was a cow with extensive tuberculosis of the udder. The milk had been supplied by the farm in an unpasteurised condition to the working-class population at the mill.

Although examination failed to reveal bovine tubercle bacilli

in the infected individuals in any of these outbreaks, there cannot be any doubt as to the correctness of the diagnosis. In 1936 a very severe outbreak was observed by STÅHL (121) in the village of Horred. The source of infection was a cow affected with tuberculosis of the udder. Bovine tubercle bacilli were found not only in the milk but also in the gastric lavage from one of the patients. Not less than 50 persons were infected, 25 of whom developed morbid symptoms. Three of the latter had hilar lymphoma (one of them also erythema nodosum), 3 had tuberculosis of the mesenteric lymph nodes, 2 erythema nodosum only, 2 erythema nodosum and cervical lymphoma, 10 cervical lymphoma only, 2 pharyngitis and 3 an increased rate of sedimentation (without local symptoms). A similar outbreak was observed by KÄLLER (55) in the Province of Värmland. Several persons in the same neighbourhood became ill with fever and hard, painless swellings up to the size of walnuts at the mandibular angles. Some of the infected individuals showed changes only on one side of the neck, the tonsil on the affected side being frequently observed to be more swollen and reddened than that on the opposite side. In the majority of the cases the radiography of the lungs showed normal conditions; the patients' general condition was not affected although they had a rather high fever for some days. A detailed report was given of 15 cases with tuberculosis of the cervical lymph nodes, of which not less than 8 also had had erythema nodosum. Bovine tubercle bacilli were found in the gastric lavage from two of the patients. Another epidemic, occurring in the Province of Värmland, has been observed and described by OLSSON (79). The source of infection was tuberculous cows, from which bacillus-containing milk had been sold. The affection was diagnosed in July 1937; within a week not less than 21 cases of tuberculosis of the lymph nodes and erythema nodosum being found in children, between the ages of 2 ½ and 18 years, living in two villages with a population of altogether 2,000 inhabitants. The symptoms were fatigue, listlessness, fever, occasionally sore throat, vomitings and indefinite abdominal trouble. Two of the cases had headache and stiff-neck. Some days after the onset of the illness hard and painless lymph nodes, varying in size from a hazel-nut to a hen's egg, appeared on the neck. Erythema nodosum occurred in 8 cases either alone or in association



with tuberculosis of the cervical lymph nodes. In 3 of the children the radiogram showed suspected parenchymal changes, 9 children had somewhat enlarged or condensed hilar regions or enlarged lymphomatous shadows. Subsequent investigation revealed not less than 58 cases manifesting signs of fresh tuberculous infection. Of these, 21 required sanatorium care. One of the children later on developed exudative pleurisy. Bovine tubercle bacilli were found in 2 of the children. GNOSSELIUS (32) has reported a similar epidemic, which took place in Gothenburg, where 136 persons belonging to 33 families had consumed unpasteurised milk. Of 100 persons tested 98 gave a positive tuberculin reaction. Of these not less than 23 must be regarded as having certainly been infected by the milk. Two had erythema nodosum, 7 tuberculous cervical nodes. Bovine tubercle bacilli were demonstrated in two cases. The same milk had been supplied to a summer-home for 42 children, of whom at least 17 were infected. Of these 17 infected children 4 had erythema nodosum and 7 tuberculous cervical nodes.

Epidemics of bovine tuberculosis in man are therefore by no means rare, and they should in future be studied very carefully so as to increase our knowledge of primary bovine tuberculosis. Valuable information about the symptoms and clinical features of this disease, however, may also be obtained by studying cases that do not occur epidemically. Thus JENSEN (53), in collaboration with BLEGVAD, for instance, has described 15 cases of primary conjunctival tuberculosis caused by the bovine type of bacillus. This form of the disease is characterised by conjunctival tuberculosis of the eye and enlargement of the pre-auricular lymph glands on the same side.

The clinical picture of bovine primary tuberculosis in our material was the following: When the *primary lesion* was situated in the *abdomen*, other tuberculous manifestations often occurred at the same time, and their symptoms then dominated the picture of the disease. Thus, for instance, in Cases 11 and 12 miliary tuberculosis and tuberculous meningitis occurred also, in Case 13 tuberculous meningitis, and in Cases 16 and 17 tuberculous peritonitis. The symptoms and the clinical picture were the same as in the corresponding disease of human origin. In *primary tonsillar tuberculosis* (Cases 20 and 23) the tonsils were hypertrophied and tuberculously changed.

The lymph nodes on the same side of the neck were also greatly enlarged. All patients affected with *primary tuberculosis of the lung and hilar region* (Cases 2—10 and 15) felt ill. They very often complained of cough, fatigue and fever, occasionally of stitches and stabbing pains in the chest. A few of the cases had also intestinal disorder of very short duration. The rate of sedimentation was almost regularly greatly increased. In 8 of the 10 cases changes in the lung and in the hilar region on the same side (a primary complex) were observed at the same time. Two of these cases showed also radiological signs of atelectasis. In the remaining 2 cases only hilar adenitis occurred.

To sum up it may thus be said that as a rule primary bovine tuberculosis, like the human type, manifests symptoms of disease, which vary however to a certain extent according to the location. If the first tuberculous changes are found in the abdomen, the usual symptoms are pain in the abdomen, nausea, vomiting and loose stools. If meningitis, miliary tuberculosis, peritonitis, etc. develops, however, the symptomatic picture is dominated by these affections. If the primary tuberculosis is localised in the throat, the symptoms will be throat disorder and enlargement of the cervical lymph nodes. In primary conjunctival tuberculosis ocular symptoms and enlargement of the pre-auricular lymph nodes are observed, while in a pulmonary localisation cough and stitch in the chest may occur. Common features in all these forms of primary tuberculosis, however, are a more or less marked effect on the general condition, fatigue and an increased rate of sedimentation. Erythema nodosum is a very common occurrence, and must therefore be regarded as a very important symptom also in primary bovine tuberculosis. *There is obviously no essential difference between primary bovine and human tuberculosis either as regards symptoms or the clinical picture otherwise.*

d) *How long is the interval between bovine primary tuberculosis and the appearance of secondary and tertiary tuberculous changes?*

As in human tuberculosis, it is of exceedingly great interest to ascertain the interval between the manifestation of the primary

bovine tuberculosis (primary lesion) and the appearance of secondary and tertiary tuberculous changes in man. If the primary changes are fresh, it is a rather easy matter to determine this interval. It is much more difficult, however, if only old residues of the primary lesion remain, for in such a case it is impossible to know for certain whether these rests (calcified primary lesion, calcified lymph nodes in the hilum or in the abdomen, etc.) like the present changes are really due to bovine bacilli. There is a possibility that these rests were caused by human tubercle bacilli, but that the primary infection had healed, thereby enabling the bovine bacilli to produce changes. Such an explanation, however, must be regarded as rather unlikely, at any rate it must be a rare occurrence. Besides, there is no reason to suppose that a primary bovine infection in man heals more readily than that caused by the human type of bacillus. We can therefore feel rather sure that the rests of an earlier tuberculosis met with so very often in the bovine cases, especially when they are localised to the abdominal nodes, are as a rule due to bovine bacilli. But the age of such residues of a primary tuberculosis is difficult, indeed impossible, to determine, and consequently in such cases the interval can be estimated only approximately.

We shall now see what information is afforded by my cases on this point. Only 21 of them can be used for this purpose. In addition to secondary or tertiary tuberculous changes all of them show either an existing primary tuberculosis or rests of such an affection, thus enabling me to determine the interval with a certain degree of accuracy.

In 10 of the 21 cases the interval between the primary infection and the secondary or tertiary tuberculosis varied from some weeks up to 2 years. Of these cases 2 (Cases 11 and 12) developed miliary tuberculosis and meningitis almost immediately after the primary abdominal tuberculosis. The same thing applies to one case of meningitis (Case 13) and 2 cases of peritonitis (Cases 16 and 17). In one case of bone tuberculosis (Case 27) there also occurred serious abdominal symptoms indicating a relatively fresh alimentary tuberculous infection, from which the osseous changes developed by haematogenous metastasis. All these cases were children, 2 of whom were 6 years of age, the others being between 7 months

and 2 years old. The interval was somewhat longer in Case 7 (14 years of age), who had a tuberculoma, and in Case 4 (aged 10 years), who developed secondary pulmonary tuberculosis, the tuberculoma and the pulmonary lesions appearing about a year after the primary bovine changes in the lung and hilar region respectively. In Case 15 (aged 41 years) an exudative pleurisy occurred 17 months after the manifestation of erythema nodosum and a primary complex in the lung and hilar region. In Case 10 (aged 30), however, the primary complex was particularly malignant. In this case the lung lesion progressed after the lapse of a very short interval. New changes appeared in the lungs, causing the patient's death already 13 months after the detection of the primary tuberculosis.

In the remaining 11 cases the interval must have been very long, assuming that the calcifications demonstrable at the same time as the fresh changes were of bovine origin. Of these 11 cases, 10 were adults, the remaining case being a child aged 12. It is worthy of note that 2 of them were 62 and 68 years of age respectively. Thus in some of these cases the primary changes may have been several decades old. Nothing more definite can be said on the matter. Calcified lymph nodes were found in the abdomen in 2 cases of renal tuberculosis (Cases 35 and 36) and in 4 cases of pulmonary tuberculosis (Cases 52, 53, 55 and 67.) On the other hand, a calcified primary complex in the lung, or calcifications in the lung or in the hilar region occurred in 2 cases of renal tuberculosis (Cases 34 and 38), in 1 case of bone tuberculosis with abscess (Case 28) and in 2 cases of pulmonary tuberculosis (Cases 47 and 51).

There can hardly be any room for doubt that bovine tubercle bacilli — in exactly the same manner as the human type — can produce secondary or tertiary changes in man either immediately or shortly after the primary infection or later on in life. *The latent period of bovine tuberculosis, that is, the period between the probable original infection and the appearance of different forms of secondary and tertiary tuberculosis, may therefore vary from a few weeks up to several decades.*

*c) What is the clinical picture of secondary and tertiary tuberculosis (of bovine origin) in man?*

As far back as 1911 it was conclusively shown by the British Royal Commission on Tuberculosis that bovine bacilli were able to cause all the chief forms of human tuberculosis, including tuberculous meningitis and ulcerative pulmonary tuberculosis. Bovine pulmonary tuberculosis, however, was considered to be very rare. Thus, according to GRIFFITH (39), up to 1930 no case of phthisis pulmonalis definitely attributable to infection with bovine tubercle bacilli had been discovered in foreign countries, though sputum examinations in 926 phthisical cases had been reported. On the other hand, in England 3 (or 1 per cent) out of a total of 327 phthisical persons had been found to be expectorating bovine tubercle bacilli. For Scotland the figure was higher, where the bacilli had been typed in altogether 468 phthisics. Of these not less than 18 (about 4 per cent) had bovine tubercle bacilli in the sputum. Since then more and more cases of bovine pulmonary tuberculosis have been reported, but up to 1937 the total number of bovine phthisical cases in Great Britain amounted to only 194. Subsequent investigations, especially in Denmark, have however disclosed a surprisingly large number of such cases. In the southernmost part of Sweden (in the Province of Skåne), too, this form of disease is by no means rare, as appears from the present investigation.

The different forms of bovine tuberculosis in man agree well with those we are accustomed to see after infections with human tubercle bacilli. GRIFFITH (41) writes: »It is clear that the bovine tubercle bacillus can produce all the different forms of clinical tuberculosis and can set up tuberculous lesions in every organ and gland indistinguishable from those caused by the common human tubercle bacillus». This view is shared by a great many investigators (see GERVOIS), and corresponds well with the observations made in this work.

As appears from Table 6 (p. 128), a great many different tuberculous manifestations could be shown in the examination of tuberculous persons in Skåne. In no case was it possible to show any definite divergency from corresponding changes attributable to human bacilli. I have already been able to show the good agreement between the clinical picture of primary bovine tuberculosis

and that of human origin. But also secondary or tertiary tuberculosis does not present any distinguishable feature from human tuberculosis of the corresponding type. As is evident from the large number of reproductions inserted, it is of very great interest to note that the radiological picture of bovine pulmonary tuberculosis is exactly the same as that of pulmonary tuberculosis of human origin. The malignancy of the phthisical cases, however, is especially noteworthy. Thus not less than 19 of the 28 cases of bovine phthisis were predominantly exudative, two of them (Figs. 21 and 23) showed even gross pneumonic changes. Cavities were found at the time of diagnosis in 20 of the cases. Only 12<sup>1</sup> of the 28 cases are still alive, the others died, in spite of all therapy, as a rule in the first or second year after the disease had been diagnosed. Bovine pulmonary tuberculosis is therefore no less malignant than human phthisis. Nor was the prognosis of the other forms of tuberculosis — as may be seen from the clinical analysis — more favourable than that of corresponding forms of tuberculosis due to the human tubercle bacillus.

*Thus secondary and tertiary tuberculosis of bovine origin in man agrees completely in its clinical picture with the human type.*

### *f) How is bovine tuberculosis diagnosed?*

Since bovine tuberculosis in man does not differ in any of its forms from human tuberculosis, being on the contrary indistinguishable from the latter in its appearance, development and course, it is impossible to base the diagnosis on the clinical picture. Nor is any aid obtained in this respect from tuberculin tests. KAISER (55) reports that he obtained a somewhat stronger reaction with bovine tuberculin than with human in patients affected with bovine tuberculosis, but the material was so small that he did not draw any definite conclusions from the result. He is of opinion, however, that tuberculin tests may have a certain significance in cases of fresh tuberculous infection. On the other hand, ZIELER (134), working with a larger material, came to the conclusion that testing with different tuberculins is an entirely valueless method. »Nur durch

<sup>1</sup> At the time of printing 2 more cases, Cases 44 and 45 have died from their tuberculous disease.

Prüfung mit Kultur- und Tierversuch kann festgestellt werden, ob eine Hauttuberkulose des Menschen durch den Typus humanus oder den Typus bovinus hervorgerufen ist». DADDI (20) also states that he did not find any significant difference in tests with different tuberculin.

A few isolated tuberculin tests were also carried out in my investigation for the purpose of ascertaining whether there was any difference in the reaction between human and bovine tuberculin in patients affected with bovine tuberculosis. The tuberculin tests were made by the cutaneous method of Von Pirquet. Two tests were performed in all experiments. It goes without saying that both the human and the bovine tuberculin were of the same strength. Tests were made on 7 cases of fresh bovine tuberculosis. Of these cases, 2 (Cases 2 and 8) had erythema nodosum and a primary complex in the lung and hilar region, 2 (Cases 3 and 4) had erythema nodosum and hilar adenitis, 1 (Case 39) had renal tuberculosis and phthisis (primary infection about 2 years previously), while the remaining 2 cases, denoted by a and b in the table (brother and sister of Case 2), had a fresh tuberculous infection. Examination, however, failed to reveal bovine tubercle bacilli in the two last-mentioned cases and they have therefore been omitted from the present series (see Case 2 in Case Histories). Finally, a tuberculin test was also made in one case (Case 45) of bovine pulmonary tuberculosis, in which the primary infection had taken place at some time unknown in the past. The result of the tests is shown in the following table.

As appears from the Table 11, the difference in the mode of reaction even in these cases — although most of them were fresh — was not great enough to warrant the use of the tuberculin test in the differential diagnosis between human and bovine tuberculosis. Some of the bovine cases were even more sensitive to human than to bovine tuberculin.

*The only reliable method at present for distinguishing between bovine and human tuberculosis is by typing the tubercle bacilli, i. e. by cultural methods and animal experiments.* That being so, it is of the greatest importance that typing of the bacilli is also performed as often as necessary. In localities where tuberculosis of cattle is rare this method need only be applied in exceptional cases. On the other

Table 11.

Case No.	Human tuberculin		Bovine tuberculin	
	Redness mm.	Papule mm.	Redness mm.	Papule mm.
2	15 × 15	8 × 8	14 × 14	7 × 7
	15 × 14	7 × 8	13 × 14	6 × 7
3	11 × 12	6 × 6	14 × 14	8 × 8
	17 × 16	10 × 11	14 × 13	7 × 7
1	22 × 16	11 × 9	11 × 12	7 × 8
	25 × 25	9 × 10	10 × 8	8 × 6
8	16 × 15	9 × 10	12 × 10	6 × 7
	10 × 10	8 × 7	12 × 10	8 × 8
39	25 × 25	15 × 15	20 × 25	12 × 10
	20 × 20	12 × 15	18 × 18	10 × 8
a	15 × 15	10 × 8	14 × 13	11 × 10
	20 × 20	15 × 10	12 × 15	8 × 8
b	20 × 20	10 × 8	16 × 15	11 × 8
	25 × 20	10 × 10	6 × 7	5 × 4
15	10 × 12	8 × 8	12 × 14	8 × 10
	10 × 10	8 × 6	12 × 12	10 × 10

hand, if tuberculosis of cattle is wide-spread, the bacilli should be typed in all cases of tuberculosis in man. In that way the nature of the disease can be clarified. It is not less important, however, that information is obtained which may lead to the elimination of the source of infection. Typing is therefore a very important measure in the fight against tuberculosis.



#### 4. Summary.

A report is given of 67 cases of bovine tuberculosis in man, observed in the southernmost part of Sweden (the Province of Skåne) during the years 1936—1939. During the recording and collation of the data a further 27 cases were diagnosed, therefore *the total number of known bovine cases in Skåne at present amounts to 94*. Most of these tuberculous cases and all the *pulmonary* tuberculous cases were met with in the County of Malmöhus. *The number of cases of primary, secondary and tertiary pulmonary tuberculosis of bovine origin amounted to not less than 42, corresponding to a little more than 3 per cent of the typed specimens from patients with pulmonary tuberculosis*. While the work was being collocated a further 11 cases were detected. Thus altogether 53 cases of pulmonary tuberculosis in man have been discovered in the Province of Skåne (v. Pag. 152).

Of the 67 cases 33 were males and 34 females. The material contains only a small number of children, otherwise the figure for the bovine cases would have been much higher. The reason for this is that the main purpose of the investigation was to ascertain the incidence of *pulmonary* bovine tuberculosis in Skåne. The typing of the bacilli was therefore as complete as possible only in so far as pulmonary tuberculosis is concerned. The bacilli were also typed in other forms of tuberculosis, but not to so great an extent. Thus, of the 67 cases recorded only 8 belonged to the age-group 0—4 years and 11 to the age-group 5—14 years. The other 48 cases are distributed rather evenly among the age-groups up to 42 years, becoming fewer in the following age-groups. In 3 of the cases bovine tuberculosis was diagnosed as late as 62–68 years of age.

Only 14 of the 67 cases were found in persons living in towns, and of these 14 several had acquired their bovine infection during

an earlier stay in the country. The remaining 53 cases occurred among the rural population. As the population of Skåne at the end of 1938 amounted to 773,363 persons, 326,338 living in towns and 447,025 in rural districts, it is evident that the rural population is exposed to a greater risk of infection. Persons, whose occupations bring them into a more regular and direct contact with cattle (veterinarians, butchers, farmers, tenant-farmers, cowmen, farm-servants, farm-labourers, and their wives and children), run a great risk of being infected. Not less than 43 of the 67 cases belonged to this category.

The bovine source of infection could be shown in 15 cases. In the majority of these cases the tuberculous changes were fresh, and therefore no great difficulties were encountered in tracing the source of infection. On the other hand, this failed, with but few exceptions, in those cases in which infection had taken place some time in the past.

In 32 of the 67 cases other members of the family had previously manifested or were still manifesting signs of tuberculosis, which in some cases was of bovine origin, in others of human origin.

The tuberculous cases have been divided, according to the nature and location of the changes, into 10 groups (v. Table 6, p. 128), which are discussed in detail. *Group 1* contains 1 case without any demonstrable changes but with bovine tubercle bacilli in the gastric lavage, while *Group 2* comprises 9 cases showing hilar or pulmonary changes, or both, occurring simultaneously with or shortly after the primary tuberculous infection. Thus, infection in the latter cases was caused by the inhalation of tubercle bacilli. As the result of the primary infection 4 of these cases had erythema nodosum and a primary complex, 2 had erythema nodosum and hilar adenitis and 3 a primary complex (without erythema nodosum). Three of these patients were children of the same family. Bovine tubercle bacilli were found once in the sputum, 4 times in both sputum and gastric lavage, 3 times only in the gastric lavage and once in the pleural fluid and the lung tissue (at necropsy). In 6 cases the source of infection was tuberculous cows, in 1 case an elder sister affected with bovine phthisis, and in 1 case tuberculous material at a veterinary laboratory. In the remaining case the source of infection could not be discovered.

The appearance of the primary bovine changes is illustrated by Figs. 1—9. One of the cases subsequently developed secondary pulmonary tuberculosis with bovine tubercle bacilli in the sputum. Two of the patients died about a year after the primary infection, one from a bovine tuberculoma of the cerebellum, the other from a haematogenous dissemination to other parts of the body. *Group 3* comprises 2 cases of miliary tuberculosis and tuberculous meningitis, *Group 4* contains 1 case of tuberculous meningitis. All were children and they all died after a short period of illness. In one case the source of infection was tuberculous cows, but inspection failed to reveal the source of infection in the other two cases. Tubercle bacilli were found in the cerebrospinal fluid. *Group 5* includes 2 cases of exudative pleurisy, both adults. Tubercle bacilli occurred in the pleural exudate. In one case the source of infection was tuberculous cows, in the other it could not be discovered. *Group 6* is comprised of 2 cases of tuberculous peritonitis. Both were children, who died shortly after the onset of the disease. Bovine tubercle bacilli were found in the mesenteric lymph nodes (at necropsy). The source of infection in both cases was tuberculous cows. *Group 7* consists of 7 cases of tuberculosis of the cervical lymph nodes, two of whom had at the same time tuberculous changes in the tonsils. In one of these cases there also occurred hilar adenitis and a transient pulmonary infiltration as well as phlyctena. Five of the cases were children, the other two were young adults aged 17 and 21 respectively. One of the patients died from miliary dissemination to other parts of the body about 10 months after the detection of the disease. In one case the source of infection was tuberculous cows; in the other cases the origin of the infection could not be discovered. Bovine tubercle bacilli were found in the lymph nodes in 3 cases, in the tonsils in 2 cases and in the gastric lavage in 2 cases. *Group 8* is comprised of 5 cases of bone tuberculosis, 2 being children, the others adults aged 20, 29 and 62 respectively. In these cases the source of infection was not discovered. In 4 cases bovine tubercle bacilli were found in the abscess punctate and in one case in the punctate from the knee-joint. One of the patients died about 4 months after the disease had been diagnosed. *Group 9* contains not less than 10 cases of urogenital tuberculosis, all adults. The tuberculous changes had

the following locations: right epididymis (1 case), kidney and bursa tuberositas tibiae (1 case), kidneys (8 cases). One of the last-mentioned cases had also pulmonary tuberculosis. In 3 of the cases the right kidney was at first affected, in 4 cases the left kidney. In 2 cases tuberculous changes were found in both kidneys simultaneously. Up to the present only one of the patients has died. The source of infection was not found in any of these cases. Bovine tubercle bacilli were shown in the urine in 8 cases, in pus from the pyonephrotic sac in 1 case.

The greatest interest is of course attached to the cases of secondary and tertiary pulmonary tuberculosis. *Group 10* contains 28 such cases, one being a girl, aged 12 years, the others adults. The source of infection, tuberculous cows, could be detected in only 2 of the cases. Bovine tubercle bacilli were cultivated from the sputum in 23 cases, from the sputum and lung tissue in 1 case, from the sputum and the pleural fluid in 1 case, from the sputum and the mesenteric lymph nodes in 1 case, and from the gastric lavage in 2 cases. The pulmonary changes were, when diagnosed, right-sided in 8 cases, left-sided in 8 cases, and bilateral in the remaining 12 cases. The extent of the changes in the lungs varied considerably. Thus in 13 cases the dissemination in the lungs was slight, in 9 cases rather extensive and in 6 cases very extensive. Not less than 19 of the 28 cases were markedly exudative, 2 of them having even gross pneumonic changes. In 20 of the cases cavities were present. *Of the 28 cases only 12<sup>1</sup> are still living*, the others died, in spite of all therapeutic measures, as a rule in the first or second year after the disease had been diagnosed.

*The tuberculous changes in the various groups did not differ in their appearance or course from those in corresponding forms of human origin. In view of the fact that not less than 26<sup>1</sup> of the 67 patients have already died it is obvious that bovine tuberculosis in man is a serious affection, which must be fought with all available means.*

The author then goes on to discuss certain important questions in the light of the observations made by other investigators. The conclusions drawn, some of which have already been mentioned, may be summarized as follows:

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<sup>1</sup> At the time of printing 2 more cases (Cases 44 and 45) have died from their tuberculous disease.

1. Bovine tubercle bacilli as a rule enter the human body by the ingestion of milk or meat from tuberculous cattle. The primary changes are therefore most frequently met with in the abdomen (tuberculosis of the mesenteric lymph nodes) or in the lymph nodes of the neck (tonsils). Bovine tubercle bacilli may, however, be introduced into the skin or the conjunctiva along with bacillus-containing dust, thus giving rise to tuberculosis of the skin or primary changes in the eye and pre-auricular lymph nodes on the same side. *It should also be borne in mind that the first changes may also occur in the lung and hilar regions by the inhalation of bovine tubercle bacilli. The surprisingly large number of such cases in the present investigation goes to prove that this route of infection is much more common than was formerly supposed. Laboratory infection, too, has been observed. Further, bovine infection can be transmitted from man to man and from man to cattle.*

2. Primary bovine infection most frequently occurs during childhood. The rural population is more frequently infected with bovine tubercle bacilli than the urban population. Persons whose occupations bring them into more regular contact with cattle are especially exposed to the risk of infection. Bovine tuberculosis in man is therefore essentially a rural problem.

3. Primary bovine tuberculosis as a rule produces morbid symptoms, somewhat variable according to the location of the changes. If the changes are localised to the abdomen, the usual symptoms are pain, nausea, vomiting and loose stools, which are occasionally predominated, however, by symptoms of meningitis, miliary tuberculosis or peritonitis. In primary cervical tuberculosis, throat trouble and enlargement of the cervical lymph nodes are met with, in primary conjunctival tuberculosis, eye trouble and enlargement of the pre-auricular lymph nodes are the dominant symptoms, while in the pulmonary localisation of the first changes the symptoms are cough and stitch. In all these localisations the patient's general condition is affected, there is lassitude, and the rate of sedimentation is increased. Erythema nodosum is also a very common symptom. Thus, primary bovine tuberculosis does not differ from the human type either as regards the symptoms or the clinical picture otherwise. (Figs. 1—9 and 41).

4. The latent period of bovine tuberculosis, that is to say, the period between the original infection and the appearance of different forms of secondary or tertiary tuberculosis, varies from a few weeks up to several decades.

5. Secondary and tertiary tuberculosis of bovine origin in man also show complete agreement with the corresponding forms due to the human type of bacilli (Figs. 10—37 and 40).

6. As bovine tuberculosis in man does not occur in any form differing from human tuberculosis, in fact its entire appearance, development and course agree closely with the latter, the diagnosis cannot be made on the clinical picture. Nor can it be made by testing with different tuberculins (bovine or human). The only possibility of establishing the diagnosis is by typing the tubercle bacilli, and that should be the standard method in areas where tuberculosis of cattle is common.

7. Since bovine tuberculosis in man has been proved to be a serious disease, it is imperative that the campaign against tuberculosis in cattle is carried on with the greatest energy. The goal must be the extermination of tuberculosis in cattle. In Sweden we have advanced far on the road to this goal. According to the working plan drawn up tuberculosis in cattle will be fought with still more energy and step by step the disease will be entirely eradicated. We are justified in believing that bovine tuberculosis in man will be gradually but inevitably stamped out in this country. For the present, however, our vigilance should not relax, on the contrary, the present investigation has clearly proved that it must be increased still further, especially in those localities in which bovine tuberculosis is still common. A regulation should perhaps be laid down that all new cases of tuberculosis in man should be typed. The technique of typing the bacilli presents no difficulty and therefore such an examination could be organised relatively easily. In my opinion it is also to be desired that the existing regulations governing pasteurisation of the milk supplied to towns and communities where the Public Health Act is in force should be made to apply also to rural districts, unless the milk originates from non-tuberculous herds. A great step in the right direction would then be made if veterinarians and doctors cooperated more closely

in the fight against bovine infection. The regulation concerning the compulsory notification of detected cases of tuberculosis of the udder should be strictly observed, and all persons known to have consumed the milk of such infected cows should be subjected to examination at a dispensary.

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The investigation into the occurrence of bovine tuberculosis in man in Skåne has been accomplished in close cooperation between doctors and veterinary surgeons. To my lot has fallen the task of giving an account of the clinical manifestations of bovine tuberculosis in man, a task which I hereby consider that I have fulfilled. The reader will have, however, noticed that certain questions have been left unanswered in my work. One should have liked to know a little more about the technique and the results of the typing of the bacilli, of the incidence and distribution of bovine tuberculosis in Skåne, of the measures already taken and those which should be introduced in future to combat this disease, which has been shown to be of such great importance to man. I have intentionally refrained from touching upon these questions, as they belong to that part of the work which LINDAU and MAGNUSSON have to deal with. For the discussion on these matters the reader is therefore referred to their works, which will also be published in *Acta medica Scandinavica*.

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THE RELATION BETWEEN BOVINE  
AND HUMAN TUBERCULOSIS FROM  
THE VETERINARY POINT OF VIEW

BY

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## Introduction.

The investigations carried out under the auspices of the Swedish National Society Against Tuberculosis have now been completed as regards the incidence of bovine pulmonary tuberculosis among the population of the Province of Skåne. When planning these investigations we had at first thought it possible, as already done in Denmark, to map out the cases and to show that a certain relationship existed between the geographical distribution of the detected cases and the frequency of bovine tuberculosis within that area. It also became gradually evident that there was a topographical connexion between tuberculosis in man and in cattle in so far that the majority of cases of individuals infected by the bovine bacillus were found among the rural population occupied in tending cattle. A small number of cases was found in towns, but some of them had previously resided in the country. The greater part of the material consisted of persons above 15 years of age who had not lived all the time in the same district, and in these cases it was not possible to establish when and where they got their infection. In these latter cases no connexion could of course be established with extensive bovine tuberculosis in a certain district.

The smaller part of the material comprises children whose place of residence was easy to control. The material was so small, however, that it could not be shown that any particular area was more dangerous for human beings, as far as tuberculous infection is concerned, than another. Herds with numerous cases of open tuberculosis are still spread practically all over the province, and the cases of bovine tuberculosis in children were shown to be due to the

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ingestion of tubercle bacillus-infested milk or to contact in various ways with tuberculous animals on the farms at which they were living.

As the eradication of bovine tuberculosis is the most important prerequisite for the prevention of the spread of bovine infection to man, my report will in the first place be devoted to the incidence and the combating of bovine tuberculosis in all its different phases, especially in the Province of Skåne.

To illustrate the sources of infection I have included a history of those cases where the Medical Board considered that a veterinary inspection should be made in the environment in which the patients had been found. Several illustrative examples will be given of cases in which both children and adults were exposed to massive infection.

At the same time I have tried to show the various steps taken by the public authorities to diminish the risk of infection from tuberculous cattle to human beings, and I have endeavoured to call attention to the shortcomings still existing in this respect.

In view of the fact that cases were known in which infection had been transmitted from tuberculous patients to tuberculosis-free herds, the proposed scheme had also included a special investigation as to the possibility of infection being transmitted by man in this way under natural conditions. There are two sides to this problem, however, owing to the fact that the virus may be one of two kinds, according as the human subjects have bovine or human tuberculosis. I have been in a position to give examples of both kinds. It is only recently that this point has been given due consideration, and it seems to be of great importance to veterinary surgeons and farmers in their efforts to keep their herds free from tuberculous infection. The present investigation shows that an intimate cooperation is necessary between veterinary surgeons and doctors in order to prevent as far as possible their respective clientele from infecting each other with tuberculosis.

## **The Incidence of and Campaign against Bovine Tuberculosis in Sweden.**

Nothing certain is known as to when bovine tuberculosis first appeared in Sweden. There is every reason to believe that the primitive cattle of the country were free from tuberculosis, but were

infected in the beginning of the 19th century by animals imported from abroad. Cattle were imported from Holland, Belgium, France and England by private persons and by the State for the purpose of improving the indigenous breeds. The State had established a number of stock-farms, some of which had to be discontinued owing to the extensive spread of tuberculosis among the animals. But by this time breeding animals had been placed among many previously non-infected herds. Improved means of communication facilitated the sale of livestock and animals could also be shipped to distant areas, thus resulting in the transference of virus-carriers. The rise of dairies, from which skim-milk and whey were returned to the cattle-owners for feeding purposes, also contributed to the rapid spread of tuberculosis, especially in areas with a large cattle population. It became evident that the disease was of a serious nature and was a grave menace to the entire cattle stock of the country.

It should be noted that in the 80s and 90s the problem of the interaction between bovine and human tuberculosis came into prominence, and the danger of infection from animals to man was employed to bring about the first preventive measures against the spread of the disease. The problem was also discussed for the first time at a general meeting of the Swedish Medical Association at Norrköping in 1887. A committee was appointed, which succeeded in bringing about, among other things, an orientating investigation as to the frequency of bovine tuberculosis in the country. This took place before tuberculin came into use and consequently only the occurrence of the more severe forms could be approximately estimated.

Reports were received from about 60 veterinary surgeons in different parts of the country. The frequency of tuberculosis was estimated at about 5.5 per cent. The investigation comprised approximately 23,000 cows. It was pointed out that tuberculosis of cattle was most widespread in the Province of Skåne, a part of Halland, Östergötland and Södermanland.

In a paper in the »Djurvännan», 1890, A. BERGSTRAND, Veterinary Officer for the County of Östergötland, stated that bovine tuberculosis was appallingly common and was becoming more and more wide-spread every year in the same degree as farmers pursued the policy of improving the blood and increasing the milk

yield by importing pedigree animals possessing «eminent qualities» and by treating dairy cows more like machines than organisms with independent lives. Within a short time there were not many of the large farms that could claim to be entirely free from tuberculosis.

When tuberculin testing began to be performed a few years later it very soon became evident that the disease was much more prevalent than the clinical examinations had shown, and that it was absolutely necessary that preventive measures should be introduced by the public authorities.

The first steps were taken by the State in 1894, when funds were granted for the production of tuberculin, which was to be supplied to veterinary surgeons willing to participate in the work of eradicating tuberculosis. A plan of organisation for the campaign was worked out and in 1897 a Veterinary Inspector was appointed to conduct the tuberculosis campaign under the direction of the Board of Agriculture. The uncontrolled import of tuberculous cattle was stopped in 1898 by the introduction of quarantine regulations. These prescribed that all cattle imported from abroad must have passed the tuberculin test.

The anti-tuberculosis measures were entirely voluntary, with the exception of those relating to tuberculosis of the udder. According to an order issued in 1897 all animals affected with such a form of tuberculosis were to be immediately destroyed at the expense of the State. Otherwise the anti-tuberculosis campaign was organised on the same lines as in Denmark, i.e. according to Prof. B. BANG's method. By the diagnostic use of tuberculin this method involves the segregation of the reactors and the herd is afterwards restocked with only tuberculosis-free animals.

During the progress of the work it was found that tuberculosis was very wide-spread in many districts, especially those in which the cattle population was high and in which the most valuable breeding stocks were situated, the number of reactors in the large herds often being as high as 100 per cent. Under such circumstances the sacrifices were too great to enforce the carrying out of the necessary measures. The campaign against tuberculosis by the application of the BANG method was therefore pursued chiefly in those provinces in which the frequency of bovine tuberculosis was low and among herds, the owners of which were finan-

cially well off, and where there was sufficient stall-space to isolate the animals.

Even in 1932, i. e. after 35 years' work, there were in the whole of Sweden not more than 5,999 herds comprising 159,802 animals subjected to tuberculin control. This was an exceedingly small part of the total number of cattle in the country, for in the County of Malmöhus alone there were 20,000 herds consisting of approximately 250,000 head of cattle.

In the years 1898—1907 the average number of reactors in herds tuberculin tested for the first time amounted to 30.1 per cent for the entire country. The corresponding figures for the counties of Malmöhus and Kristianstad were 57 per cent and 38.9 per cent respectively. During the period 1908—1932 the number of reactors in the whole of the country decreased to 20.8 per cent, in the County of Malmöhus to 39.8 per cent and in the County of Kristianstad to 34.9 per cent. Thus a slight improvement could be ascertained.<sup>1</sup>

In 1910 only 90 herds consisting of 6,901 cattle in Malmöhus and 18 herds consisting of 679 cattle were tuberculin tested. Breeding animals purchased from the Province of Skåne for areas up the country were not infrequently found to be severely affected with tuberculosis, and animals from the province began to fall into disrepute as being highly tuberculous. This led the Agricultural Society of the County of Malmöhus to direct the campaign along another line. A method tested in Germany, the OSTERTAG method, was applied. This method involved the slaughter of animals affected with tuberculosis in an infectious form and rearing the young animals isolated from the older ones. The object of this new injunction was to endeavour gradually to build up an entirely non-reactive herd. The examinations were carried out by veterinary surgeons appointed for the purpose, and a special tuberculosis laboratory was established. A similar scheme was adopted by the Agricultural Society of Östergötland County in 1925.

The endeavours to achieve freedom from tuberculosis by means of this new form of voluntary campaign did not, however, meet with much success. The method proved to be too expensive both for the Agricultural Societies and for the animal-owners. Whether they had non-reacting or clinically examined animals, the latter did not

<sup>1</sup> REGNÉR, *Handledn. etc.*, Uppsala, 1935.

receive sufficient compensation for the sacrifices they made except in certain cases, as for instance, for rearing and selling breeding animals or the production of children's milk from non-reacting cows.

Owing to the danger of foot-and-mouth disease an order was issued by the State in 1915 that all milk supplied in the counties of Malmöhus and Kristianstad for feeding purposes should be pasteurised, and this measure contributed to a good extent in preventing the spread of bovine tuberculosis by dairy milk. The regulation was afterwards made to apply to the whole of central and south Sweden and was established by the Pasteurisation Act, 1925 and 1936, the main purpose of which was now to prevent the spread of tuberculosis.

On account of the almost complete standstill in the campaign against tuberculosis, bills were repeated introduced into parliament and a few investigations were carried out by committees appointed by the State. These resulted in the exceedingly important and comprehensive Tuberculosis Act of 1934, which led to a complete reorganisation of the anti-tuberculosis work. According to this Act the State granted much larger subsidies than formerly to the anti-tuberculosis campaign amongst cattle. Finally, the most important ordinance of all came into force in 1937, i. e. the one prescribing that a certain additional price should be paid by the dairies for milk from herds belonging to the National Anti-tuberculosis Campaign.

The retrogression, stagnation or progression of the anti-tuberculosis campaign has always in the long run depended on economical factors. If the animal-owner receives compensation for his losses he is always prepared to cooperate to the fullest extent. That Sweden seems in recent years to be able to solve the tuberculosis problem so successfully — in a Report presented by the Royal Medical Board in 1940 it was shown that the number of non-reacting animals at the beginning of 1940 amounted to 50 per cent of the total number of cattle in Sweden, while the corresponding figure 5 years previously was only 20 per cent — is undoubtedly due to ample State grants and the use of the Central Price Regulating Fund in furthering tuberculosis work. This Fund is derived from the taxation of imported concentrated foodstuffs and of the margarine industry together with the higher price paid for milk for consumption as compared with milk for production, i. e. milk used

for the production of butter and cheese. Grants are made from this Fund to the different dairies, but to qualify for such a grant an extra price must be paid per litre to suppliers whose herds are under State tuberculosis control.

In South Sweden the number of tuberculosis-free herds was greatly increased owing to the fact that many animal-owners purchased non-reacting animals with the compensation they received for the tuberculous ones slaughtered during the epizootics of foot-and-mouth disease.

Another factor that has also contributed lately in improving the situation, as far as the anti-tuberculosis is concerned, is the increased knowledge of the danger of infecting human beings. From the 1st July, 1939, the sale of milk for human food, other than pasteurised milk, unless it came from herds under State tuberculosis control, was prohibited in towns or in rural districts to which the regulations of the Public Health Act applies.

A technical improvement in the tuberculin tests has been employed for the past 10 years, and that has greatly facilitated the fight against tuberculosis. Formerly the so-called subcutaneous test was almost exclusively applied, the tuberculin being injected subcutaneously in a dose varying between 15 and 50 eg in 10 % solution according to the size of the animal. The temperature was taken before the injection and also on 6 different occasions at intervals of 2 hours, beginning 8 hours after the injection. This was a tedious method, requiring the veterinary surgeon to be in attendance for nearly 24 hours. The test at present employed almost everywhere is the intradermal test, 5 eg of tuberculin in 50 % solution being injected into the skin itself. The thickness of the skin at the site of injection is measured before and 72 hours after the injection. The method is at least as reliable as the subcutaneous test and the work can be accomplished in a much shorter time than that required for the latter test. Without this simplification and improvement of the method it would have been impossible to carry out the mass examinations with tuberculin made during the past 6—7 years by the small body of veterinary surgeons in Sweden.

Preventive immunisation methods have also been tested. The most widely known is probably the BEHRING method. The vaccine used consists of human tubercle bacilli, which, as known, are not

pathogenic for cattle. This method was found to be dangerous in the case of milk cows, as the inoculum was excreted with the milk. Moreover, the protection produced proved to be insufficient and therefore quite naturally the whole thing got no further than the tests.

Greater hopes and interest were aroused by CALMETTE's vaccine, which consisted of attenuated bovine bacilli. This vaccine was injected subcutaneously in a dose of 5 cc into new-born calves.

A grant from the foundation »Therese & Johan Anderssons Minne» enabled JUNDELL and the author to carry out tests on a number of herds and on some calves specially purchased for the purpose. The method was found to be entirely harmless, and a considerably immunity could be induced in the animals. But complete efficiency could by no means be obtained. Massive infections broke down the immunity. The greatest disadvantage in practice was that the calves had to be fed on boiled or pasteurised milk during the first months after the vaccination, before the vaccine had taken effect, and had to be kept completely isolated. This became too expensive and difficult, and the calves did not do well on heated milk. This method, we presume, has now been abandoned not only in Sweden but also in other countries.

The campaign against tuberculosis is at present being carried on by two different methods.

One method, the *Ostertag method*, which aims at preparing the soil for a complete eradication of tuberculosis, is applied by the Agricultural Societies of the counties in which bovine tuberculosis is most common. By means of systematic, clinical examinations efforts are made in the first place to detect animals suffering from tuberculosis in an open form at as early a stage as possible and to slaughter the affected animals. These examinations are carried out by specially appointed veterinary surgeons at the laboratories of the Agricultural Societies under the direction of the Royal Medical Board. Main attention is directed to pulmonary tuberculosis, which is the most common form of open tuberculosis, but careful search is also made for animals affected with tuberculosis of the uterus and of the udder. Animals found suffering from such open forms of tuberculosis are immediately slaughtered at the expense of the State. Owing the expenses involved, examinations of the lungs

can be performed only once or twice yearly. On the other hand, a general sample is taken of the milk for examination from two to four times a year.

To cover the cost of this Tuberculosis Control the State contributes the same amount as that the cattle-owner has to pay the Agricultural Society. This fee varies from 2 kronor to 2.50 (2 s. 4 d.—3 e.) per animal.

After the first examination and the removal of animals with open tuberculosis, the State compensates the animal-owner for a certain part of the loss incurred in being compelled to sell for slaughter any animals found in subsequent examinations to be affected with open tuberculosis. The maximum contribution paid by the State in such a case is 50 kronor (£ 2:18:0). But if the cattle-owner, in addition to this clinical tuberculosis control, also rears the young animals isolated from adult animals, the compensation for slaughtered animals is increased to a maximum of 75 kronor (£ 4:8:0). The aim is therefore to increase the interest of the owners of cattle in the tuberculin examinations and by that means to accomplish a complete eradication of bovine tuberculosis. The method has been of great importance in anti-tuberculosis education and as a transitory method. The compensation paid by the State for these clinical examinations and for slaughtered animals suffering from open tuberculosis amounted in 1939—1940 to approximately 1,100,000 kronor (£ 64,896)..

The other method, *the Bang method*, is employed in herds and in areas in which tuberculosis has only a slight extent. By this method tuberculin tests are performed to discover all animals infected with tuberculosis, whether they are infectious or not. All reactors must be separated from the herd, but they need not necessarily be slaughtered. This phase of the campaign is directed by the Royal Medical Board. The State supplies tuberculin free of cost and pays the veterinary surgeon who performs the tuberculin tests at the rate of 5 kronor (5 s. 10 d.) per herd and 0.50 (7 d.) kronor per animal tested. The herd owner, however, must pay the veterinary surgeon's travelling expenses. If any reactors are found in a herd a re-examination may be made within 9 months at the expense of the State. If no reacting animals are found in two successive examinations the State defrays the cost of control examinations only after long intervals,



from 1 ½ to several years, varying in different parts of the country. Under certain conditions the State also pays a certain compensation for the slaughter of animals reacting to the tuberculin test and found to be affected with tuberculosis in an infectious form.

The total State expenditure in 1939—40 on the anti-tuberculosis campaign by the BANG method amounted to 846,000 kronor (£ 49,911). In addition to the direct payments to the participators in the tuberculosis work, they also receive, as mentioned above, a higher price for the milk they supply to the dairies. This additional price has amounted to at least 0.4 öre (0.22 farth.) per kilo in the case of a herd under State tuberculin control and at least 0.2 (0.11 farth.) per kilo in the case of a herd under clinical tuberculosis control. Certain dairies pay a much higher bonus and have in that way achieved a greater eradication of tuberculosis in their respective areas. To hasten the transition to non-reactivity in the herds the additional price for the two kinds of milk has now been fixed up to 0.6 (0.33 farth.) and 0.3 öre (0.11 farth.) respectively.

At present practically half the cattle stock of the country, or about 1,500,000, is affiliated to the Bang method. The 6 northernmost counties and the Island of Gotland are almost free from bovine tuberculosis, and in several other counties, particularly in the south-eastern parts of the country, the eradication of the disease has advanced far, while in other counties only 17—25 per cent of the herds are under tuberculin control.

In those parts of the country in which tuberculosis is more widespread the OSTERRAG method is applied, about 250,000 cattle over 2 years of age in 17 counties being associated.

These figures refer to the beginning of 1940. At the time of writing, one year later, no survey figures for 1940—41 are yet available, but they are certainly much higher.

In 1940 there was a considerable shortage of fodder, which necessitated the slaughtering of a considerable number of cattle. The authorities held the view that the anti-tuberculosis campaign should in the first place be kept in sight in this process of decreasing the cattle population. Thus in October 1940 the State granted a sum of 500,000 kronor (£ 24,498) for the eradication of tuberculosis among small herds in the areas belonging to 10 different Agricultural Societies. As a result many new herds have been brought into the anti-tuberculosis campaign.

On the representations of the Royal Medical Board and the Board of Agriculture it was decreed that from the 1st of July 1940 the tuberculosis campaign in certain areas of the country should be compulsory and not voluntary as hitherto. In respect to tuberculosis the country has been divided into 3 different areas: 1. tuberculosis-free, 2. protected, and 3. other areas. In the first two areas the law relating to epizootics shall also apply to tuberculosis. This implies compulsory notification of all detected cases of bovine tuberculosis, compulsory tuberculin testing and the slaughter of reacting animals. In the protected areas the anti-tuberculosis campaign will be carried on as hitherto but more intensively. The importation of animals not controlled with respect to tuberculosis is prohibited. Systematic tuberculosis eradication will be carried on in other areas so that they can be transferred to the group of protected areas as soon as possible.

It is therefore quite evident that the campaign against bovine tuberculosis has made tremendous progress and that the results already achieved give us reason to hope that before many years have passed the disease will be completely eradicated, as has already happened in Norway, Finland and most of the United States of America.

In the present survey of the cases of bovine pulmonary tuberculosis in man in the Province of Skåne, it will of course be of interest to examine more closely the most commonly occurring sources of infection. From the tuberculosis map below it will be seen that Skåne, although not the worst, is still one of the provinces in which bovine tuberculosis is common. At present 30 per cent or more of the cattle have been tuberculin-tested and belong to entirely non-reacting herds. Improvement is taking place very rapidly, as will be seen from the graphic table, Fig. 1, showing the number of herds affiliated to the Bang method during the years 1900—1940.

Thus in the two counties of Skåne the number of tuberculin-tested animals in 1920 amounted to only about 9,000 but in 1932 the number had increased to 20,000 and in 1940 to more than 111,000.

The number of animals in Skåne to which the OSTERTAG method is applied is about 50,000.

Conditions vary very much in the different parts of the pro-

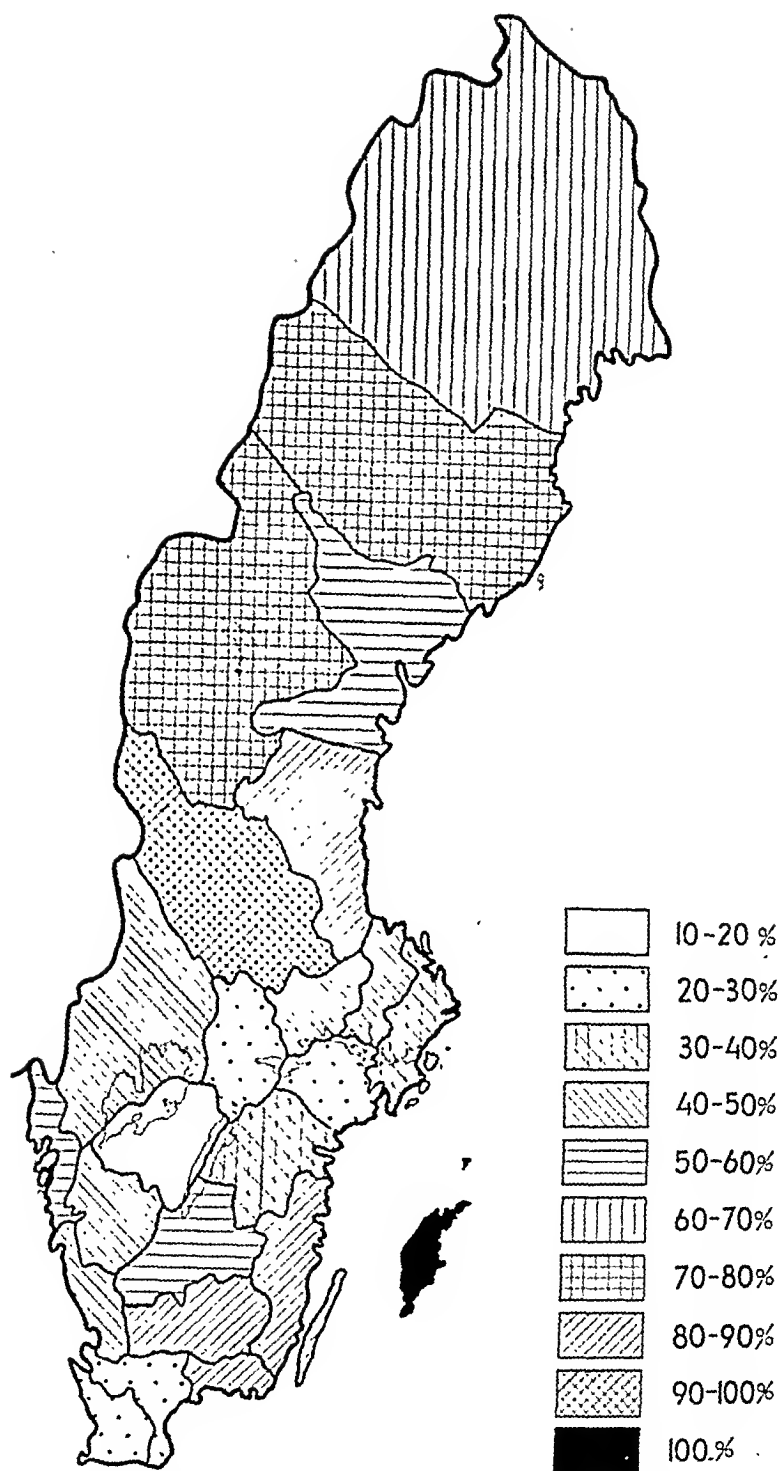


Fig. 1. Tuberculosis map of Sweden showing the number of cattle in the entire country belonging to the State Tuberculin Examinations in 1940. The percentage figures denote the known number of non-reacting animals. It will be seen from the map that the Province of Skåne is still one of the most tuberculous provinces in the country.

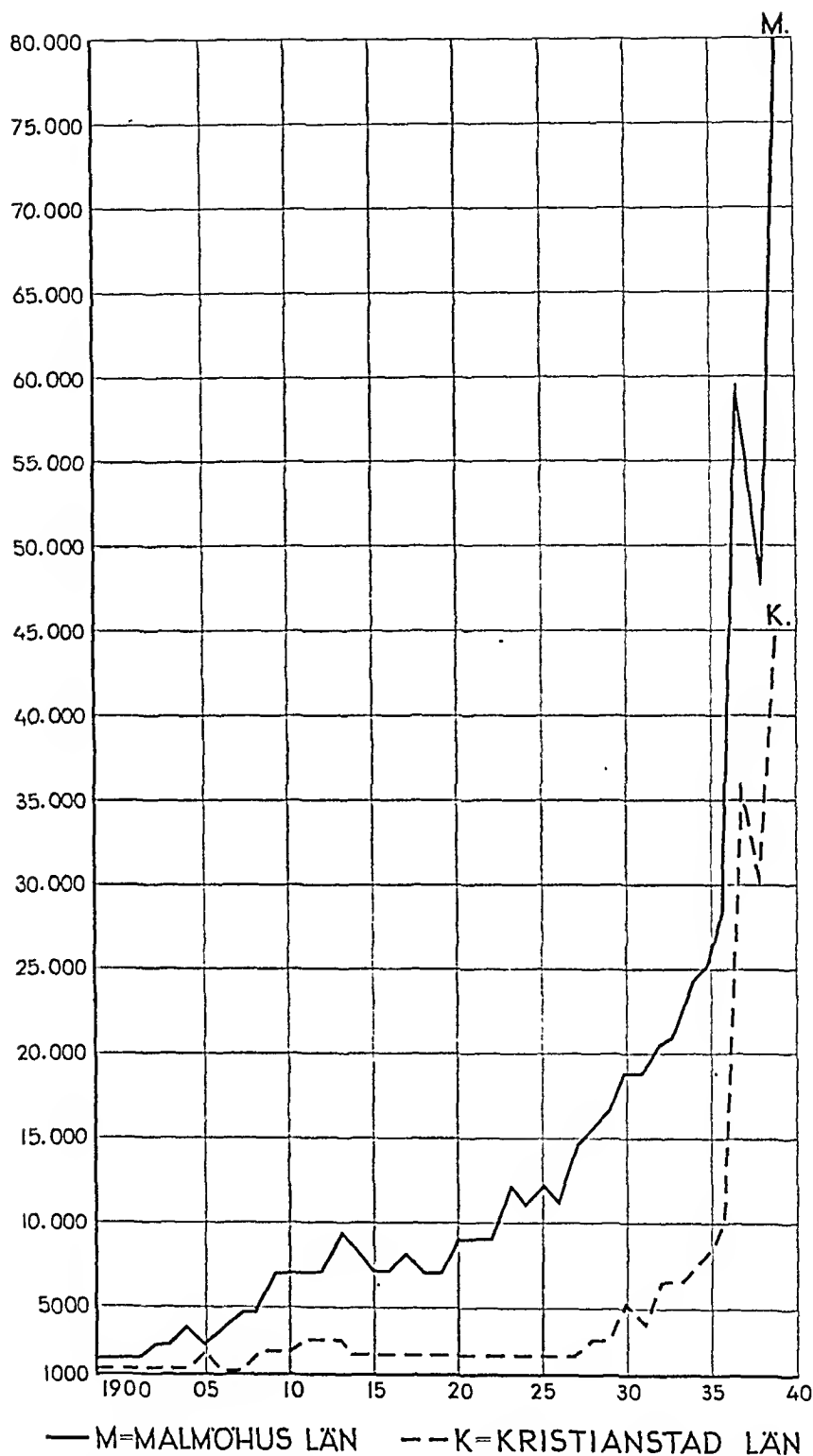


Fig. 2. The graph shows the number of herds belonging to the anti-tuberculosis campaign according to the BANG method in the two counties of the Province of Skåne from the beginning of the century up to 1939. The curves denote the number of tuberculin tested cattle in the different years. It will be seen that after 1935 the campaign was greatly intensified. The declining tendency in 1938 is due to the appearance of foot-and-mouth disease, when the tuberculin tests had to be discontinued for some time in Skåne.

vince. There are districts in which over 50 per cent of the cattle are under tuberculin control, but there are others in which only 15—20 per cent are included in the campaign.

### The commonest sources of infection in bovine tuberculosis.

The possibility of human beings being infected by the bovine bacillus is much greater in country districts than in towns. The agricultural population is exposed to *milk*, *contact* as well as *inhalation infection*. On the farms unpasteurised milk is consumed. The rather numerous herds that are still not subjected to tuberculosis control constitute a risk of infection not only for those families whose members come into direct contact with the animals but also for other categories of people working on the farm. In towns and villages, on the other hand, the danger of such an infection may be said to be very slight, owing to the fact that the milk supplied by the dairies is pasteurised, unless it originates from tuberculosis-controlled cows.

The transmission of infection by other animal foodstuffs than milk certainly does not play any rôle. Meat inspection is now carried out almost everywhere and special attention is paid to tuberculosis.

The frequency of the sources of bovine infection can be estimated from the reports of the Public Abattoirs and Controlled Slaughter-houses, the official reports of tuberculosis of the udder and the genital organs and the information supplied by the Dairy Associations as to the quantity of milk controlled with respect to tuberculosis compared to non-controlled.

From the following table, showing the extent of tuberculosis in the different slaughter-houses, it will be seen that tuberculosis was found in 22—47 per cent of the carcasses of cattle examined. It should be noted, however, that most of the cases were slight, a tuberculous focus being found in the lung or in the cervical lymph glands.

The most dangerous forms of open tuberculosis in our cattle are tuberculosis of the udder and of the urino-genital organs. These forms were much more common in the County of Malmöhus than in

*The frequency of tuberculosis at the Abattoirs and Controlled Slaughterhouses in the Counties of Kristianslad and Malmöhus during 1921—1939.*

Year	County of Kristianstad			County of Malmöhus		
	Tuber- culosis	Number of cattle slaught- tered	Percent- age	Tuber- culosis	Number of cattle slaught- ered	Percent- age
1921—1925	4,043	12,933	31.3	46,880	125,292	37.4
1926—1929	3,818	11,406	33.5	45,712	125,327	36.8
1930—1933	9,792	30,451	32.2	47,139	132,964	35.5
1934—1936	11,234	35,911	31.3	34,397	101,268	34.0
1937—1939	16,134	55,780	28.9	43,506	126,495	34.4

the County of Kristianstad. The average number of cases of tuberculosis of the udder reported in the County of Kristianstad was 0.15 per mille and in the County of Malmöhus 0.22 per mille.

The average number of cases of uterine tuberculosis recorded in the County of Kristianstad was 0.19 per mille, in the County of Malmöhus 0.41 per mille. These figures, however, do not give a true picture of the actual incidence, for many cases are never detected and reported.

In the large and medium-sized herds, before the animals have been clinically examined and the affected ones eliminated, open pulmonary tuberculosis occurred in about 5—10 per cent of the adult animals over 2 years of age. Inoculation experiments on guinea-pigs with mixed milk from such herds gave positive results in 5—10 per cent, and with mixed milk from clinically controlled herds in 1—2 per cent.

Persons living in an environment in which no measures are being taken against bovine tuberculosis may be assumed to be strongly exposed to bovine infection, especially in the case of large or medium-sized herds.

In recent years the different dairies have formed themselves into so-called Dairy Associations, and they carefully control the quantity of milk received from tuberculosis-controlled herds. In 1939 not less than 37.5 per cent of the milk supplied to these dairies was tuberculosis-controlled, and in 1940 it amounted to 42.4 per cent. Particulars from 4 different dairy associations in the Province of Skåne are given in the following table.

*Milk production under tuberculosis control according to data supplied by the Dairy Societies of Skåne in 1939 and 1940.*

*The figures show the supply during one of the autumn months.*

Dairy Societies	Year	Total in kilos	Tuber- eulin control	%	Clinical control	%	Clinical+tu- bereulin control in per- centage of total
South-western....	1939	25,069,148	3,942,900	15.7	2,895,410	11.6	27.3
	1940	20,531,857	4,632,481	22.4	2,520,715	12.3	34.7
South-eastern ....	1939	13,787,673	2,100,803	15.2	2,699,985	19.6	34.8
	1940	11,657,481	2,718,194	23.3	2,377,819	20.4	43.7
North-western....	1939	13,535,908	4,339,971	32.1	2,360,402	17.4	49.5
	1940	11,648,962	4,385,244	37.6	2,008,776	17.2	54.8
North-eastern ....	1939	10,153,238	1,905,567	18.8	1,970,671	19.4	38.2
	1940	7,187,155	1,838,258	25.5	1,158,220	16.1	41.6
The whole of Skåne	1939	62,545,967	12,289,241	20.5	9,926,468	17.0	37.5
	1940	51,025,455	13,574,177	26.6	8,065,530	15.8	42.4

The table shows the quantity of milk delivered to the dairies in Skåne in 1939 and 1940 also the amount of that milk supplied from non-reactive and clinically examined herds. At present 26.6 per cent of this milk can be regarded as free from tubercle bacilli and 42.4 per cent under State control, either by means of tuberculin tests or clinical examinations. *Thus, 57.6 per cent of the dairy milk is still outside the tuberculosis control.*

The present investigation showed that cases of bovine pulmonary tuberculosis in man were not met with in the County of Kristianstad, whereas 63 cases were found in the County of Malmöhus. This great difference, however, does not correspond to an equal difference in the incidence of bovine tuberculosis in the two counties. It is true, the percentage of non-reacting and clinically controlled herds is higher and the number of cases of tuberculosis of the udder and genital organs lower in the County of Kristianstad than in the County of Malmöhus, but the difference is not so great as might be expected from the number of human cases. At first sight it might be supposed that a map of the human cases would show that they occurred chiefly in areas with intensely infected herds, as K. A. JENSEN showed to be the case in Denmark. The number of human cases was too small in Skåne, especially in the





County of Kristianstad, to furnish figures that would topographically fit in with the high figures for the incidence of bovine tuberculosis in different parts of the province. As already pointed out by HEDVALL, some of the patients have changed their domicile in the province, and it is conceivable that they obtained their bovine infection in another environment than that in which it was detected and long before the anti-tuberculosis campaign in Skåne was so far advanced as it is at present.

### The possibilities of infection in human and bovine tuberculosis.

The relation between human and bovine tuberculosis is to a certain extent complicated, owing to the existence of different types of bacilli, to which human beings and cattle show different degrees of immunity. In both species three different types of tubercle bacilli have been observed. With regard to these three types the present view is that the prevalent type in cattle is the *bovine tubercle bacillus*. It is also known that, provided the possibilities of infection are equal, the bovine type is as virulent for man as for cattle. That it is generally not so dangerous for man, however, as the human type is certainly due to the circumstance to which BRUNO LANGE and K. A. JENSEN called attention, i. e. that it occurs less frequently as an inhalation infection with a primary complex in the lungs but as an alimentary infection with a primary complex in the digestive canal, especially in the cervical and mesenteric lymph nodes. Inhalation infection requires an infinitely smaller number of tubercle bacilli to bring about malignant infection. It frequently occurs in man, however, in surgical tuberculosis in children, and still more frequently in pulmonary tuberculosis than was formerly supposed.

The human type is by far the most important in man, but cattle show a striking immunity to this type. Only a few cases of focal tuberculosis in cattle caused by human bacilli are known. Reports of cases of slight tuberculous processes, especially in the lymph nodes of the digestive organs, have been published in Holland, Denmark and also in Sweden. In order to obtain accurate information as to the effect of human tubercle bacilli on cattle

under the same conditions as an infection is assumed to take place among herds, PLUM infected 3 cows and 4 calves by feeding them with sputum from man infected with the ordinary human type of bacillus. Six months later only one of the calves showed macroscopically demonstrable changes. These changes were found in the mesenteric lymph nodes. All the animals, except one cow, gave a positive tuberculin reaction 1 ½ months after the beginning of the feeding. All attempts made so far to demonstrate human bacilli in the milk from cattle thus infected have failed.

*The avian type* has been very seldom shown in man, but it may occasionally attack cattle, being found in the lymph nodes and in pregnant cows, in which it produces a tuberculous metritis with subsequent abortion. It also produces tuberculin sensitivity, which is particularly marked, however, to avian tuberculin.

In view of the harmlessness of the avian type for man, it need not be taken into account in the problem of the interaction between human and bovine tuberculosis.

The behaviour of the bovine type is quite different, for it acts in both directions. We have already mentioned the danger of man being infected by the bovine type of bacillus, to which sufficient attention has not been paid until recent years.

The other side of the question, i. e. where cattle are the objects exposed to infection, was not considered to be urgent until it became known that bovine tuberculosis in man was more common than was supposed.

Although it was quite natural, theoretically, that persons infected with the bovine bacillus were as dangerous to their environment as tuberculous cattle, it was nevertheless conceivable that passages with a long sojourn in the human body would reduce the virulence of the bovine bacilli for cattle so that they were no longer as dangerous as the genuine bovine type. To test this experiments were also carried out by PLUM with sputum from phthisical patients. Two cows and three calves were fed with doses considered to be approximately equivalent to the quantity of sputum expectorated during a long period by a phthisical patient when tending a herd. The result of these experiments was that all the animals developed macroscopically demonstrable tuberculosis. Sensitivity to tuberculin occurred already after 3 weeks.

*To sum up it may be said that cattle can infect man only with the bovine type of bacillus, whereas man can infect cattle with both the bovine and the human types of bacilli, but not with the avian type.*

As a rule, it cannot be ascertained by means of the tuberculin test whether cattle are infected with human or bovine tuberculosis. The effects of the tubereulin, whether produced from bovine or human tuberele bacilli, are practically equivalent. In some instances it has been alleged that human infection produces a somewhat more powerful reaction to human tubereulin than to bovine tubereulin; but in general this difference in degree is so slight and uncertain as to be of no practical importance. In Finland the incidence of bovine tuberculosis being very low (STENIUS and HINDERSON) they have a much more extensive experience of human infections in cattle, and in that country the human virus from such cases has caused a reaction in herds that had been non-reactive for a long time. Infection with avian tuberele bacilli, which is still more common than human infection, has also frequently a disturbing action. When the tuberculin reactions are doubtful, re-tests are made in Denmark and Sweden with both bovine and avian tubereulin. If a stronger reaction is obtained with avian tubereulin, the only step taken is to remove the avian source of infection, after which no further reactions occur. Avian tuberculin gives about twice as strong a reaction as bovine tubereulin if avian tuberculosis is present.

On the other hand, if such a difference in degree is not obtained, the possibility of a human infection or an incipient bovine infection must be taken into account. In such cases a double normal dose, 30—100 eg, of bovine tubereulin, is injected subcutaneously into all the animals to find out whether they give a definite or doubtful reaction. If an animal that previously gave a positive reaction to the intradermal test also reacts to the subcutaneous test, a bovine infection is considered to be present. In human infection, on the other hand, it will be found that only some of the animals that reacted to the intradermal test give a positive reaction to the subcutaneous test, while some of those that gave no response to the subcutaneous test give reactions to the intradermal test. Steps are then taken to try to discover and eliminate the source of infection. In human infection, as



Fig. 4. A farmer's family of 7 children (Case 1; Hedvall's Cases 2—4), 6 of which developed bovine tuberculosis at a definite time. The picture shows the parents and 4 children. The other 3 children are at the hospital. The eldest daughter, and the youngest, aged 12 and 7 months respectively when the infection took place, are seen in the centre. The youngest child, who had not been in the cow-stall nor given milk from the affected cows, was the only one that was not infected.

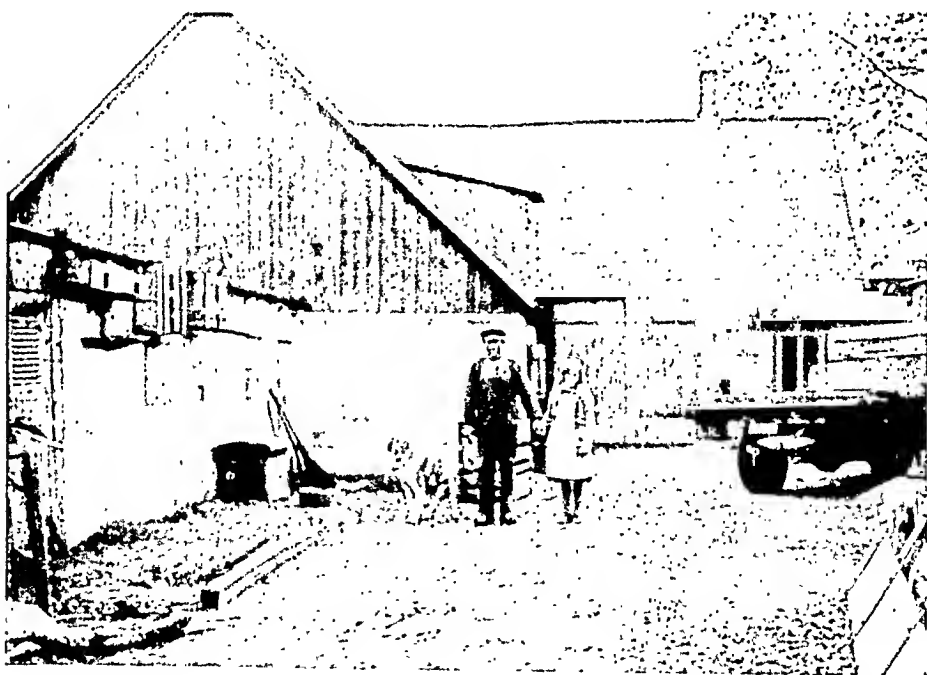


Fig. 5. View of the farm. The cow-house, which was only about 15 yards from the dwelling-house, was much frequented by the children. Of the small herd of 5 animals 3 cows had open tuberculosis. One of them had tuberculosis of the udder.



in avian, the reactive power of the cattle often disappear after some months, if the source of infection has been removed from the farm.

But in the case of persons infected with bovine bacilli or such an infection from tuberculous cattle, strong reactions will occur at least in some cases, and these reactions will persist if retests are made. If the double test does not produce a definite reaction, some of the least valuable animals are slaughtered for *post-mortem* examination. The finding of a focal tuberculosis indicates the presence of bovine infection. Human and avian infections very seldom give rise to any demonstrable changes. Cultures are made and inoculation experiments are also performed on guinea-pigs and rabbits with specimens from the lungs and lymph nodes, especially if lesions are found in these organs.

## Case Histories.

### Cases of bovine infection from cattle to man.

#### *Cases in children.*

*Case I.* (Fig. 4, 5) The most pregnant example of the transmission of infection from cattle to man is furnished by a crofter's family. This family consisted of 7 children, of which no less than 6 became ill at about the same time. Bovine tubercle bacilli were found in 3 of them (HEDVALL's Cases 2—4). The family were poor and lived on a farm of about 14 acres. The father was incidentally employed in driving the milk from the neighbouring farms to the dairy. There was a small herd of 3—4 cows, the cowstall being situated at a distance of only about 10 metres from the dwelling-house. The hygienic conditions were the worst possible. The father groomed and fed the animals and the mother did the milking. The children were between the ages of 7 months and 12 years, and all of them, except the youngest, used to accompany their parents to the cowstall, where they liked to carry on their games. All the children, except the youngest, were given raw milk from the herd every day. The children were very fond of being in the cowstall, because it was often warmer there than in the house. The farm is situated in a lonely spot, exposed to cold winds, especially during the spring and winter.

An inquiry into the health of the herd revealed that a cow with open pulmonary tuberculosis still remained on the farm and that in the months immediately prior to the outbreak of the affection there had been two cows in the herd that had to be slaughtered in the following autumn owing

to tuberculosis. One of these animals had an advanced pulmonary tuberculosis and the other acute tuberculosis of the lungs, the kidneys, the udder and the uterus.

It can therefore be assumed that there were abundant tubercle bacilli within the comparatively small cowstall and that the children were exposed daily to massive infections not only by the milk but also by inhalation and by contact.

*Case II.* A child, aged 15 months, had died from acute miliary tuberculosis and tuberculous meningitis caused by bovine tubercle bacilli (Hedvall's Case 12). The father had been a groom and the mother a milkmaid for a herd of 12 cows. The owner had sold 6 of these animals for slaughter, when it was found that 3 of them were affected with open pulmonary tuberculosis. As far as is known, no case of tuberculosis of the udder had occurred in the herd. The child had been given raw milk from this herd for a period of 5 months, and it is probable the bovine infection was due to the ingestion of this milk.

*Case III.* A child, aged 16 months, had died from peritoneal tuberculosis due to bovine tubercle bacilli (Hedvall's Case 16). The father had been employed as farm labourer, but neither he nor the mother had had anything to do with the cowstall. For a period of 3 months the child had been fed on raw milk from the herd, which consisted of 150 animals. A previous clinical examination of the herd had revealed two cases of open pulmonary tuberculosis. There is reason to assume that the child had been exposed to infection from the end of March to the end of June 1938. In the beginning of September one of the cows was found to be affected with tuberculosis of the lungs, the uterus and of the udder. The changes were advanced and the cow was probably infectious through the milk at the time when the child can be assumed to have got its infection. The parents had fed the child with raw milk.

*Case IV.* A child, aged 10 months, had died from bovine intestinal tuberculosis (Hedvall's Case 17), and in the beginning of April the same year a half-brother, aged 8 years, had had a lymphoma, cervical tuberculosis and tuberculosis of the bronchial lymph nodes. Bovine tubercle bacilli were found in the gastric lavage. For several months before the onset of the disease both children had been given raw milk from a large herd of about 130 cows. The family lived on the farm. The father had assisted in machine-milking the cows, but the mother had not had anything to do with the animals. The elder child had not been in the habit of entering the cowstall.

At about the same time a 1  $\frac{1}{2}$ -year-old child of another family had died from tuberculous meningitis. The bacilli were not typed. The family was otherwise in good health. This case, too, was probably due to the bovine tubercle bacillus.

In view of what had occurred the owner of the herd was induced to affiliate his herd to the State Controlled Clinical Examinations. It was found that not less than 13 of the animals had open tuberculosis. No case of tuberculosis of the udder could be demonstrated, but in view of the numerous cases of open tuberculosis in the herd it was unavoidable that the milk was contaminated with tubercle bacilli. Thus the infection in the above-mentioned cases was certainly due to the ingestion of raw milk.

*Case V.* A child, aged 2  $\frac{1}{2}$  years, had shown bovine tubercle bacilli in the stomach washing. (This case was detected later and is not included among Hedvall's series of 67 cases.) The father has a small farm with a herd of 4 cows. The child became ill in May 1939. At about the same time one of the cows in the herd was found to be affected with tuberculosis of the udder, and a little later another cow was shown to have open pulmonary tuberculosis. The child had not been in the cowstall but had been given raw milk from the cow in question. Considering the small number of animals in the herd, the concentration of tubercle bacilli in the milk shortly before the onset of the disease must have been high.

*Case VI.* On 2nd January 1940 bovine tubercle bacilli had been demonstrated in the gastric lavage of a child, aged 21 months. The child had become ill already on the 13th November 1939. (This case was detected later and is not included among Hedvall's 67 cases.)

The family lived on a farm with a herd of 24 dairy cows. The father was employed as cowman and the mother as milkmaid. Ever since the age of 10 months the child had been given raw milk from the cows on the farm. On the other hand, the child had not been taken inside the cowstall. A clinical examination in May 1940 revealed that one of the cows was suffering from tuberculosis of the udder. This cow had also an old tuberculous pneumonia. On the 1st of January 1940 another cow had to be sold owing to illness, probably tuberculosis.

*Case VII.* A female, aged about 15 months, (Hedvall's Case 18) had tubercle bacilli of the bovine type in the gastric lavage on 15th December 1937, and the mother and two more children of the family were found to have signs of an old abdominal tuberculosis, probably of bovine origin. The child had not been in the cowstall and the parents had not tended cattle, but they had obtained milk from a herd in which there had been several cases of open tuberculosis. Thus on 5th June 1937 a cow belonging to this herd was found to be affected with open pulmonary tuberculosis. An examination of a sample of the mixed milk taken on 9th July revealed the presence of tubercle bacilli. On 23rd October it was proved that the tuberculous milk originated from a certain cow affected with tuberculosis of the udder.

*Case VIII.* After an illness lasting only 14 days, a male, aged 4 years, had died from bovine tuberculosis localised in the abdominal cavity and



meninges (This case was detected later and is not included among Hedvall's 67 cases). For two years before the child became ill, the parents had been living on a farm. The farmer was employed as working farm-foreman and the mother as milkmaid. The child had been allowed to accompany the mother to the cowstall and remain there while she milked the cows. The family received 4 litres of fresh milk from this herd daily, and this milk was always ingested raw. The herd was evidently highly infected with tuberculosis, and a cow sent to slaughter a few months before the onset of the child's illness was found to be so extensively affected with tuberculosis, even pulmonary tuberculosis, that the carcass had to be entirely condemned.

A clinical examination of 18 cows showed that no less than 6 had open pulmonary tuberculosis.

Thus the infection in this case may have taken place by contact, by inhalation and by the milk.

*Case IX.* A 14-year-old farmer's son developed bovine hilar adenitis and pulmonary tuberculosis and died one year later from a tuberculoma of the cerebellum (Hedvall's Case 7). The family history was free from tuberculosis. The herd, consisting of 3 cows, was found to be free from tuberculosis. The other children of the family were tuberculin negative. The patient, however, had lived at an uncle's farm, several miles away, for 4 ½ months. There he had been permitted to assist in tending a tethered cow, which had subsequently to be slaughtered owing to open pulmonary tuberculosis. On a tuberculin test the herd had been non-reactive but had later had a relapse owing to the fact that this cow did not react but was nevertheless infectious. No case of tuberculosis of the udder had occurred. Two cousins of the patient, aged 8 and 10 respectively, had also drunk raw milk from the herd, but gave a negative tuberculin reaction. Thus in this case it is improbable that milk infection took place, the disease occurring through contact with the phthisical cow. Inhalation infection was discovered at autopsy.

#### *Cases in adults.*

*Case 1.* A milkmaid, aged 40, had acute bovine pulmonary tuberculosis. (This case was detected later and is not included among Hedvall's 67 cases.) The patient had been a milkmaid ever since youth, but she had been employed at different farms, where no definite information could be obtained as to the frequency of tuberculosis among the cattle after the lapse of so many years. The patient had now a farm of her own. An examination of the herd gave a negative result. Two or three years before the illness, however, the patient had milked the cows at another farm, where a cow had to be sold owing to advanced tuberculosis. She had not ingested any milk from that herd.

This may possibly be a case of contact infection. It is also conceivable that she contracted the disease from the herds belonging to the farms at which she had been formerly employed.

*Case 2.* A 45-year-old farmer developed bovine pulmonary tuberculosis, from which he died after some months' illness. (This case was detected later and is not included among Hedvall's 67 cases.) As an agricultural pupil in his youth he had tended cattle on several farms. His herd consisted of 9 cows. Prior to the farmer's illness there was a cow in the herd that had to be slaughtered owing to advanced tuberculosis. In recent years, however, he had had nothing to do with tending the cattle. It is nevertheless possible that he had been infected by the milk from his own herd. It is also conceivable that he got his bovine infection by his close contact with cattle during his youth.

*Case 3.* A cattle-tender, aged 43. (This case was detected later and is not included among Hedvall's 67 cases.) A radiographic examination in June 1940 showed uncertain signs of pulmonary tuberculosis. He appeared to be in good health and had no cough. After guinea-pig inoculation and cultural experiments, the bacteriological examination of the stomach washing revealed the presence of tubercle bacilli of the bovine type. The patient's wife and 8 children showed no morbid changes. During the past 2 years, from March 1938 to the beginning of 1940, before taking up his present position, the man had been employed as cowman on a farm with a herd of some 30 cattle. The herd belonged to the Controlled Clinical Examinations. During 1938—1940 not less than 10 animals had to be eliminated owing to open pulmonary tuberculosis.

Thus the frequency of tuberculosis was unusually high in the environment in which this man carried on his work, and there must have been great opportunities for infection by inhalation and by contact. Alimentary infection can in all probability be excluded, for the patient's family, who had also ingested raw milk from the herd, did not become infected.

Owing to the fact that the milk from this farm was supplied to a sanatorium, the entirely staff was radiographically examined. The detection of the patient's tuberculous infection would certainly not have been made at such an early stage in an ordinary medical examination. He had tended the herd from March to June and also a couple of months in the autumn. The herd consisted of 118 animals and had been non-reactive for several years. But now a large number reacted, although no definite information could be obtained as to the kind of infection present. The reaction to different kinds of tuberculin did not give definite results. The investigation is being continued (See Case 2, p. 228).

### A case of bovine conjunctival tuberculosis.

*Case 4.* To complete the material of bovine infection in man in the Province of Skåne I shall also include the following rather rare case, although it was observed before the present investigation was started.

On December 3rd, 1932, Dr. JONAN HOLMSTRÖM, Malmö, sent to the authors Laboratory a sample of pus from a patient, whom he believed was infected with tuleraemia, a disease which had just begun to be spoken of at that time.

The patient was a milkmaid, aged 22, employed at a farm with an average-sized herd in the neighbourhood of Simrishamn. The herd was not subjected to any kind of tuberculosis control, and the frequency of tuberculosis among the cows may be assumed to be the usual one, i.e. about 10 per cent open tuberculosis.

The disease had manifested itself as a swelling of the pre-auricular lymph node, an inflammation of the eyelid and a granular conjunctivitis.

Microscopic examination revealed no bacteria, and cultural experiments on the usual nutrient media gave negative results. Inoculation into guinea-pigs and rabbits produced severe tuberculosis. The high degree of virulence of the bacilli for rabbits indicated that they were of the bovine type, which was also confirmed when they were typed at the State Serum Institute, Copenhagen.

The case was briefly reported by Dr. M. HOLMSTRÖM in the «Svenska ögonläkarnas förhandlingar» (Transactions of the Swedish Ophthalmological Society), 1933.

Only a few such cases are known in Sweden, and the only ones in which the type of infecting bacillus was determined were of human origin (2 cases reported by SAMUELSON and GRANSTRÖM).

According to BLEGVAD, 40 cases of conjunctival tuberculosis have been recorded at the Finsen Institute, Copenhagen, up to 1935, and all those in which the bacilli were typed (11 cases) were of bovine origin.

### Cases of tuberculous infection of the human type from man to cattle.

*Case 1.* In a herd of about 20 animals no reactions had been obtained to the tuberculin tests made in October 1938 and in June 1939. In the autumn of 1939, however, a cowman employed on the farm became ill and on admission to the Lung Clinic of Lund Hospital in April 1940 he was found by Dr. HEDVALL to be affected with extensive, bilateral, cavernous phthisis. The rate of sedimentation remained at about 62 mm. Tubercle bacilli, which were found to be of the human type, were present in the sputum in large numbers in each field of vision. On admission to hospital the patient was febrile, but the temperature gradually fell to normal value.

On learning of his employee's infection the animal-owner became afraid that his herd may have been infected and therefore requested a re-test. This was performed in April 1940, the result being that 4 of the animals gave a positive reaction. The increase in the thickness of the fold did not exceed 5 mm. in any case. No reaction was obtained to avian tuberculin. In order to differentiate the reaction from that usually obtained

in bovine infection a subcutaneous injection of double doses of bovine tuberculin was made on the following day. None of the animals showed any rise in temperature. This non-agreement between the results of the subcutaneous and the intradermal test argued strongly in favour of the infection being due to human tubercle bacilli.

Three of the four animals that reacted to the intradermal test were slaughtered, but did not show any macroscopically demonstrable tuberculous lesion in any organ. A re-test was made 5 months later, bovine tuberculin being injected intradermally, but none of the animals reacted, not even the only remaining animal that had given a positive reaction previously.

The facts that the tuberculin reactions were slight, that three of the reactive cows did not show any tuberculous changes, that the results of the subcutaneous and the intradermal tests did not agree and that the reaction was not stable, suggest rather strongly that the infection in this case was caused by tubercle bacilli of the human type from the phthisical cowman.

*Case 2.* A similar case relating to a herd of 149 cattle, also from the Province of Skåne, has been reported by BRON ANDERSSON, Assistant Secretary at the Royal Medical Board.

The herd had been free from reactors during the years 1937—1939. In March 1940 eleven of the animals gave a positive reaction, but as all the reactions were slight the presence of bovine tuberculosis was not suspected. The herd was therefore re-tested with avian tuberculin. No evident reactions were obtained. A fortnight later a subcutaneous test was made on the entire herd, the results of which did not agree with those of the intradermal test. Three of the animals reacting to the intradermal test were slaughtered but no tuberculous foci were found in any organ. Guinea-pigs were inoculated with portions of the lungs, and the lymph nodes and with tracheal mucus at the State Veterinary Bacteriological Laboratory. The guinea-pigs developed generalised tuberculosis and typing was made with material from the lymph nodes of tuberculous guinea-pigs. Tubercle bacilli of the human type were demonstrated.

The entire staff of the farm was examined at the Central Dispensary at Lund but no case of open tuberculosis could be shown.

Thus in this case the source of infection could not be discovered. Changes very often take place in the staff of such a large farm, however, and it is therefore probable that the tuberculosis carrier no longer remained on the farm at the time of examination.

### Cases of bovine infection from man to cattle.

*Case 1.* As far as I am aware, the first observation of a case of this kind was made at a large farm in the neighbourhood of Malmö in March 1936.

The herd belonging to this farm had been non-reactive for the past

7 years. But in March 1936 not less than 49 of the 74 animals gave a positive tuberculin reaction. The infection seemed to be mostly prevalent among the cows, not less than 23 out of 37 reacting. Of the youngest calves only 2 reacted. The subsequent investigation proved that the infection of the herd was not due to any of the usual causative factors in such disasters. No animal had been purchased from abroad, and no contact had taken place with other animals. It had been entirely restocked with animals bred on the farm. That the source of infection was the dairy could be excluded owing to the fact that the calves fed on milk were practically all non-reactive. It is of course conceivable that owing to an error in the tuberculin test some animal affected with tuberculosis in an infectious form failed to be detected. But the animals sold for slaughter in the previous year and even earlier had not shown any tuberculosis, and the clinical examination made a few weeks after the tuberculin tests did not reveal any animal with any suspicious symptoms. In a subsequent investigation as to how the herd had been infected, the owner reported that one of the milkmaids had been found to be affected with tuberculosis. She had had a «cold», she said, and had been observed to cough very much during the time she was in his employ. Before her illness had been diagnosed as tuberculosis, which led to her dismissal, she had been occupied, with two other milkmaids, for about 4 hours daily during a period of about 6 weeks in milking. (Hedvall's Case 62). She had extensive tuberculous changes in the lungs and a cavity the size of a mandarin (see Fig. 32 in Hedvall's report). Bovine tubercle bacilli were found very abundantly and typed by Prof. Lindau in the sputum. She died from pulmonary tuberculosis. She began working at the farm in November 1935, i.e. 5 months before the appearance of the disease in the herd. The most obvious assumption is that the milkmaid in question was the cause of the mass infection.

The herd was so severely attacked that the application of the tuberculin method had to be abandoned. The subsequent course of the disease could not be following owing to the fact that the animals had to be slaughtered in 1938 on account of an outbreak of foot-and-mouth disease.

*Case 2.* On March 14th, 1940, a cowman was employed at a farm with a herd of 118 cattle, which supplied certified milk and had been non-reactive for quite a long time. The herd was tuberculin-tested on May 8th, 1940. This cowman had been previously employed on a farm at which extensive tuberculosis was known to exist among the cows. He milked the cows belonging to the present herd up to 12th May, i.e. for nearly two months. The animals were then turned out to graze. He resumed the work of milking and tending the herd on 15th August and continued doing so until 7th October, when he was found to be affected with pulmonary tuberculosis (see Case 3 adults, p. 225). On 25th November it was reported that the infection was due to bovine tubercle bacilli. (Lindau).

The herd was re-tested with tuberculin on 11th June, 1941, when a

large number of reactors were detected. Control examinations are being made in order to find out whether the infection was due to bovine bacilli. The increase in thickness of the fold was small, and therefore avian or human infection cannot be excluded.

## **Rules and regulations for the Prevention of the Tuberculous Infection by Milk.**

The transmission of tuberculosis from cattle to man is quite naturally believed to occur in the first place by the ingestion of different kinds of animal food-stuffs, and therefore a great many precautionary measures have been taken. The Meat Inspection Act prescribes, among other things, that meat and viscera shall be examined with respect to tuberculosis before they can be approved for human food. The control in this respect is easily carried out and can be regarded as effective in both towns and rural districts. But that cannot be said to be true as regards milk. Here great difficulties are encountered in detecting existing infection and also in introducing adequate preventive hygienic measures against the spread of such infection. Below I shall examine the public steps taken for the prevention of the transmission of tuberculosis by milk and try to point out in what respect these measures seem to be inadequate.

The Public Health Act, 1919, which applies to the whole of the country, contains the following clause: »Milk from an animal which is or can be suspected to be affected with a disease that can have an injurious effect on the quality of the milk, or has been treated with any drug, which by passing into the milk or otherwise may render it injurious or unfit for human food, shall not for that purpose be supplied to towns and there exposed to sale or delivered to another person».

From this it is clear that the animal-owner can be made responsible if he supplies milk from affected animals to the towns.

»Without the consent of the Board of Health milk shall not be offered for sale or sold under a designation implying that the milk is of a particularly sound condition or is under control in that respect.»

From this it follows that if a herd supplies, for instance, certified

milk or babies' milk the Board of Health has power to see that the products satisfy hygienic demands in every respect.

»If, owing to decomposition, uncleanness, faulty preparation or *any other cause*, food in other cases is *injurious to health* or otherwise unfit for human food, or the same has been prepared or handled by a *person* who is suffering or is suspected to be *suffering from a disease or infection* likely to render the food *dangerous to consume*, it shall not for the purpose of being used for food be supplied to a town or there offered for sale or transferred to another person.»

The above clause gives the Board of Health the power to take samples of milk supplied to towns, and if tuberculosis is met with the sale of the milk for human food can be prohibited. Further, the authorities can intervene if it is known that tuberculous persons are employed in the cow-house, dairy or milk-shop, for another clause runs as follows: »If there is good reason to assume that food of any kind and from a certain place may cause the spread of infectious disease in the town, the Board of Health may prohibit its delivery to and sale in the said town».

That the local Boards of Health can also exercise control at the place of production and in the cow-stalls is evident from the following clause: »The Board of Health may, if considered necessary, take samples for examination of any foodstuffs intended for sale, whether found at a place within the area of the Board of Health or at a place outside the said area, from where it is generally introduced to the town for sale». Much can be accomplished where the local Boards of Health organise such examinations at the place of production, and it is to be desired that this power is used more extensively.

In an Order issued by the Royal Medical Board on 7th July, 1938, regarding the requirements for the hygienic conditions in the production of milk and cream sold in an unpasteurised condition, it is prescribed that »when milking the staff should ascertain that *the animal does not show any changes in the udder or in the milk*, and that milk from animals showing such changes shall not be mixed with other milk nor used for human food without consulting a veterinary surgeon and permission for such use be obtained.»

In view of the conditions prevailing in the cow-sheds it can be safely said that such a direction affords very little assurance that

milk from cows affected with tuberculosis of the udder is not included in the milk supply. The early stages of tuberculosis of the udder are difficult to detect, and the milk often does not show any change until the process has progressed so far that the excretion of tubercle bacilli is very great. Nor can one always expect the staff to be competent enough to detect such tuberculous changes. The local Boards of Health should therefore endeavour to instruct and direct those employed in tending and milking cows in carefully controlling the health of the animals and in controlling that affected animals are not worked.

In addition to the above-mentioned public laws and ordinances there has been in existence for quite a long time a regulation, the main purpose of which is to prevent the spread of tuberculosis of bovine origin by the ingestion of milk, viz. compulsory slaughter of animals suffering from tuberculosis of the udder or the uterus. This initial measure, however, does not suffice to keep the milk free from tubercle bacilli. In order to try to trace infections occurring in human beings that may have occurred from the consumption of tubercle bacillus-infested milk, the Medical Board recently enacted that every reported case of tuberculosis of the udder shall be notified to the dispensary doctor of the district, who shall then take the necessary steps.

Unfortunately the presence of tuberculosis in milk cannot be detected so easily as in meat and viscera. Bacteriological methods are necessary, but they cannot be applied in practice because such an examination requires several weeks to accomplish. If tubercle bacilli are found in a sample of milk taken from all cows in a herd or a certain group of the herd, the laboratory shall, in accordance with the Order of 12th May 1939, notify the herd-owner, the local Board of Health, and in the event of the herd not belonging to the subsidised campaign against tuberculosis in an infectious form, also the Medical Board. The milk shall not be sold for either human or animal food without being heated until a new sample of the cumulative milk has given a negative result in a bacteriological examination for tubercle bacilli.

Our clinical methods of examination are not always sufficiently effective to show other than rather advanced cases of open tuberculosis in cattle. Tuberculosis of the udder is not the only form of open



tuberculosis that is dangerous. The difficulty is to draw a sharp boundary-line between open and closed forms. A tuberculous process may at any time become of an infectious character. It must therefore be admitted that every herd not free from reactions, even if subjected to clinical control, may be a serious source of infection. Moreover, in the open forms the tubercle bacilli frequently cannot be detected or demonstrated for certain until a long time after the animal has begun to excrete the virus, and on that account the existing regulations must be regarded as inadequate.

The situation has greatly improved by the passing of the Pasteurisation Act of the 21st July, 1937, which came into force on the 1st July, 1939. This implies that milk from herds not under State tuberculin or clinical control must be pasteurised.

On 13th November, 1940, the Medical Board decreed that milk from clinically controlled herds should also be pasteurised. This was done because it was considered that the participation in the State subsidised campaign against tuberculosis in an infectious form does not constitute a sufficient protection against the infection of human beings with tuberculosis by milk from herds belonging to the said campaign. The quantity of milk from non-reactive herds for consumption in an unpasteurised condition is at present quite sufficient to satisfy the requirements of the towns. In their proposal the Medical Board also wants to extend the measure to cover even rural districts, i. e. also for milk supplied to the staff of farms that have not passed the tuberculin test. As is clearly shown by the present investigation, there is a much greater risk of the infection being transmitted to man, especially children, by a case of tuberculosis of the udder in the cowhouse than by mixed (diluted) milk sold from a dairy or shop.

Much difficulty will be encountered, however, in putting this latter measure into practice. It will certainly take several years before it can be carried into effect, and then only when we have advanced so far that only a few tuberculin-reactive herds are left.

With regard to dairy staffs the Dairy Act, 1936, and the Tuberculosis Act, 1939, prescribe that a person employed at a dairy shall prove by a doctor's certificate, which shall not be older than 30 days, immediately before entering upon his duties that he is free

from any diseases or infection which can be transmitted to human beings by the dairy products. At least once every second year the staff shall undergo a medical examination, at the dairy's expense, for the purpose of ascertaining whether such infectious disease is present.»

A regulation has also been laid down for the purpose primarily of protecting cattle against infection by phthisical patients, but at the same time it is also a protection against the infection of milk with tubercle bacilli.

Quoting from an Order of the 15th June, 1938, from the Medical Board concerning steps to be taken in forms of bovine tuberculosis that may be assumed to be *caused by other than bovine tubercle bacilli*:

»If by means of comparative tuberculin tests or typing it has been shown that *tuberculous infection of human origin* is present in a herd, the following steps shall be taken:

The veterinary surgeon who has performed the examination shall at once notify the Medical Board thereof, who orders the medical officer of the district to examine all those members of the farm's employees, who have participated in the work in the cow-house during the past 6 months, for the presence of tuberculosis. If this examination or the examination made at the Central Dispensary reveals tuberculosis in an infectious stage in any person, he shall at once be suspended from his employment in the cow-house. If that is not done, the matter shall be reported to the Medical Board and to the Board of Health in the district from which milk from the herd is supplied or sold.»

It appears from the title of the above-mentioned circular that it really refers to infection with other than bovine bacilli. But it has already been shown above that human beings with bovine bacilli can also produce bovine tuberculosis, and therefore it is imperative that the circular in question is extended to include those cases in which the tuberculin tests and the typings of the bacilli reveal the presence of bovine infection and the route of infection cannot be definitely traced to cattle. Such cases of infection can occur in areas in which bovine tuberculosis in cattle has been completely eradicated and bovine sources of infection can be excluded. In such cases there are special reasons for trying to find the origin of the disease among infected cowmen and milkmaids.

## Discussion.

The examples given in the case histories are not numerous, but they should suffice to show the various ways in which an interaction takes place between tuberculosis in man and tuberculosis in cattle.

Most of the cases of bovine infection in man occurred among children, although only a very small part of the material sent to Prof. LINDAU for typing the bacilli originated from children. The positive results were nearly always obtained with the material of gastric lavage, thus pointing to pulmonary and tonsillar cases, but the conditions on the farms at which the cases occurred showed that 6 of the 9 cases I had an opportunity to test in this respect were due to alimentary infection alone. In two of the cases the children had frequented and played in heavily infected cow-stalls, in which there were consequently ample opportunities of acquiring dirt, contact and inhalation infection in addition to milk infection. Besides, a case of pure contact infection without simultaneous milk infection occurred in a 14-year-old boy. For several months he watered and tended a cow with advanced tuberculosis put out to graze. This was sufficient to produce in him a malignant, fatal bovine tuberculosis.

Of the adult cases the probable mode of infection was shown in only 4, three of whom were employed in tending cattle, and in which both alimentary and contact infections may have played a role. The fourth case, that of a milkmaid, was an entirely typical dirt infection. The patient developed a primary conjunctival tuberculosis.

These cases are instances of the transmission of infection from cattle to man, such as have been observed a long time ago in countries with heavily infected herds and where milk is consumed in a raw condition, but to which sufficient attention has not been paid until recent decades. Hand in hand with the progressive eradication of tuberculosis in cattle, the danger to human beings will naturally disappear. Of course we must expect to find a comparatively small number of cases for some time to come, for persons who are bovine bacilli-carriers, may live for a long time in spite of their affection, and will continue to infect their environs.

That the correlation was double-acting, there being a danger of human beings infecting cattle with bovine bacilli, was to be expect-

ed when it was found that bovine infection was not quite so uncommon among cowmen and milkmaids. Moreover, since pulmonary tuberculosis due to the human type occurs and is even more common than that caused by the bovine type, there are also possibilities of the animals being infected with both bovine and human bacilli, according to the type with which the individuals tending the cattle are infected.

Only a few cases of this kind have been discovered so far in Sweden. One of these cases was that of a milkmaid, who within a period of 6 weeks infected a large, valuable herd as extensively as if the source of infection had been a cow with pulmonary tuberculosis. We have also seen cases in which a cowman with pulmonary tuberculosis of the human type has produced tuberculin reactions, which had a disturbing effect on the judging of the situation in a non-reacting herd.

The knowledge of these facts and the increased control concerning the occurrence of tuberculosis in individuals and animals coming into close contact with one another can by means of an intimate cooperation between doctors and veterinary surgeons be of very great importance in the anti-tuberculosis work. Thus the detection of tuberculosis of the udder in a cow can inspire the search for infections in children. The occurrence of an inexplicable relapse in the tuberculin work can lead to the detection of bacilli-carrying cowmen or milkmaids. In that way it will be possible to discover patients who have not the least suspicion that they are affected with tuberculosis. In cases of tuberculosis among the agricultural population the doctors should warn both the patients themselves and the cattle-owner of the danger also of infecting the cattle. The detection of a tuberculous cowman will most likely lead to a new tuberculin examination, and in that way a new infection among the cattle will be discovered in time to prevent any great injury being done.

In one of the cases reported above, the herd-owner requested a new tuberculin examination as soon as he learnt that his employee had had pulmonary tuberculosis. Fortunately, in this case the infection was due to the human type of tubercle bacillus, and the injury caused to the herd was there slight.

On a superficial consideration of these problems it appears

as if an examination should be made of all persons occupied in the care of live-stock. That is just as reasonable as in the case of employees in dairies, for the latter can only infect the milk, while the staff of a farm can infect both the milk and the animals.

This question has also been considered by the Medical Board, but it has been rightly pointed out that such an examination cannot possibly be carried out at present, as it would involve about 300,000 persons employed in tending cattle in this country.

The task must therefore be restricted to taking steps as soon as a cowman or milkmaid is found to be affected with tuberculosis. The doctor should advise the patient to be careful in his intercourse with people but also in tending animals. He should also take samples for typing the bacilli. The result of the typing should be reported to the district dispensary for recording and supervision, and in cases of the bovine type also to the Veterinary Tuberculosis Department of the Medical Board. In that way it should be possible to follow the patients suffering from bovine pulmonary tuberculosis and prevent them from being employed as cowmen or milkmaids.

It is of exceedingly great importance that the greatest precaution is taken in those areas in Sweden in which bovine tuberculosis has already been eradicated but also in other districts where the animals are not non-reactive and the existing law does not prohibit the sale of milk in a raw, unboiled condition (infants' milk). In the former areas tuberculosis comes under »The Diseases of Animals Acts» of 1941, with compulsory reporting and slaughter of the reacting animals, therefore great losses to the public can be caused there by tuberculous persons. It is not enough to prohibit the import of living animals to these areas. Something must also be done against human tuberculosis.

When there are reasons to suspect that the herds have been infected by infectious persons, it is often a difficult matter to induce the farm-staff to submit to a thorough examination. As already mentioned, there is a defect in the present regulations, for power to require the examination of the staff is given only in cases in which the human type appears to be the cause of the tuberculin reactions in the animals. On the other hand, the regulations do not authorize compulsory examination if typical reactions indicative of bovine infection are present. Another difficulty is that the herd-owner,

if his staff refuses to submit to such a control, is perhaps afraid of giving his support as he does not want to become on unfriendly terms with his subordinates and perhaps lose them.

In the majority of cases, however, the matter can be arranged voluntarily, at least as far as the animal-owner is concerned, when he fully realises the great values he has at stake.

Besides the great danger of the herds being infected by the tuberculous staff, attention should also be called to the danger of persons with pulmonary tuberculosis infecting the milk supplied for consumption. In milking, the tuberculous person sits with the open pail in front of him beside the cow and when attacks of cough occur it can hardly be avoided that the milk is contaminated.

Veterinary surgeons and doctors can join forces in an endeavour to bring about a reform in the existing regulations both with respect to herds producing only milk for home consumption and herds supplying milk to towns and villages where the local Boards of Health have the authority to intervene.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CXXXVI

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10.6

KLINISCHE UNTERSUCHUNGEN  
ÜBER DIE HÄUFIGKEIT UND  
ART DER SEROPOSITIVEN  
SPÄTLUES IN FINNLAND

VON

*PAAVO MAIJALA*

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# KLINISCHE UNTERSUCHUNGEN ÜBER DIE HÄUFIGKEIT UND ART DER SEROPOSITIVEN SPÄTLUES IN FINNLAND

AKADEMISCHE ABHANDLUNG

VON

*PAAVO MAIJALA*  
LIC. MED., ASSISTENZARZT

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Dem Vorstand des Serobakteriologischen Instituts der Universität Helsinki, Herrn Professor Dr. med. OSV. RENKONEN, erlaube ich mir, meinen wärmsten Dank dafür abzustatten, dass er mir Gelegenheit gegeben hat, die serologischen Untersuchungen für meine Arbeit in der von ihm geleiteten Anstalt auszuführen.

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Helsinki, im Mai 1942.

*Paavo Maijala.*

## EINLEITUNG.

### Frühere Angaben über die Häufigkeit und die verschiedenen Formen der Lues in Finnland.

#### Frische Lues.

##### *A. Häufigkeit.*

Bis in die Mitte des 18. Jahrhunderts herrschte in unserem Lande ein ausserordentlich grosser Mangel an Ärzten, weshalb wir über das Vorkommen von Krankheiten vor dieser Zeit bei uns sehr schlecht unterrichtet sind. Indessen versuchten die Geistlichen, auch für das körperliche Befinden der Menschen Sorge zu tragen. So findet man in den Protokollen des Domkapitels auch Angaben über die venerischen Krankheiten. Vom 1. März 1759 an liegen bei uns mehr Nachrichten über das Auftreten dieser Krankheiten im Lande vor. Damals begann nämlich das erste Distriktskrankenhaus Finnlands in Turku mit seiner Tätigkeit, und in diesem wie auch in den entsprechenden Anstalten, die etwas später in anderen Städten gegründet wurden, fing man allmählich an, auch den venerischen Patienten Behandlung zu geben.

Bald nachdem Finnland mit Russland vereinigt worden war, ging die Regierung daran, Massnahmen zu planen, durch die die Verbreitung der Geschlechtskrankheiten verhindert werden sollte. Wahrscheinlich infolge des Krieges hatten diese Krankheiten in besorgniserregendem Grade unter dem Volke um sich gegriffen, und daraus erklärt sich offenbar die Aufmerksamkeit, die ihnen die Regierung zuwandte. Die erste Massnahme zur Bekämpfung der venerischen Krankheiten ist ein Kaiserlicher Brief vom 13.

August 1810, in dem dazu aufgefordert wurde, Krankenstuben für die Pflege venerischer Patienten zu errichten (RABBE).

Aus den Berichten über die Tätigkeit der venerischen Krankenhäuser können wir uns in grossen Zügen ein Bild von der Häufigkeit der Geschlechtskrankheiten in unserem Lande machen. Im folgenden sind die durchschnittliche Zahl der während der ersten 50 Jahre alljährlich in diesen Krankenhäusern behandelten Patienten und ihr Verhältnis (1: 10,000) zur damaligen Einwohnerzahl unseres Landes (HJELT) zusammengestellt:

Jahrzehnt	1816—1825	1246	Patienten	10.5	‰
"	1826—1835	1348	"	9.9	"
"	1836—1845	2423	"	16.6	"
"	1846—1855	2591	"	15.8	"
"	1856—1865	3704	"	21.1	"

Wir können hieraus entnehmen, in wie hohem Grade die venerischen Krankheiten damals in Finnland verbreitet waren und dass ihre Zahl im Wachsen begriffen war.

Als man später lernte, die verschiedenen venerischen Krankheiten und ihre verschiedenen Grade voneinander zu unterscheiden, erhalten wir wieder aus den Berichten über die Tätigkeit der venerischen Krankenhäuser eine allgemeine Vorstellung von der Häufigkeit der frischen Lues in unserem Lande. Abbildung 1 veranschaulicht die Anzahl der während 1910—1938 alljährlich wegen frischer Lues (Lues I und II) in die venerischen Krankenhäuser unseres Landes aufgenommenen Patienten und ihr Verhältnis je 10,000 Bewohner des Landes (nach den Berichten der Medizinalverwaltung).

Genauere Daten über die Frequenz der frischen Lues in unserem Lande gibt es jedoch erst seit Anfang 1923. In diesem Jahre machte es nämlich die Medizinalverwaltung den Kreisärzten zur Pflicht, in ihren Monatsrapporten auch Mitteilung über alle neuen Fälle von Geschlechtskrankheiten zu machen. In Abbildung 2 sind die aus unserem ganzen Lande während der Jahre 1923—1938 alljährlich mitgeteilten Fälle von frischer Lues sowie ihr Verhältnis je 10,000 Bewohner des Landes angeführt. Abbildung 3 zeigt die aus einigen Städten des Landes während 1900—1938 alljährlich angegebenen Fälle von frischer Lues und ihr Verhältnis

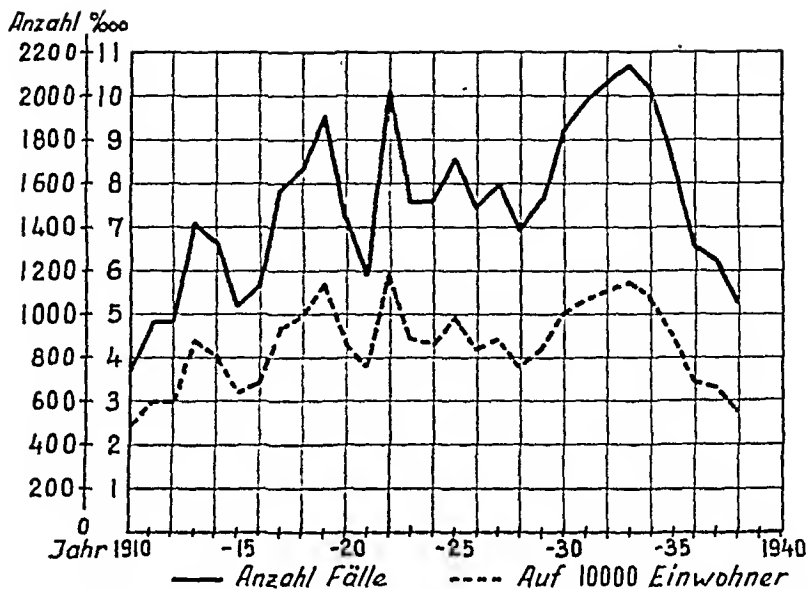


Abbildung 1. Gesamtzahl der während der Jahre 1910—38 wegen frischer Lues in die venerischen Krankenhäuser unseres Landes aufgenommenen Patienten und ihr Verhältnis je 10,000 Einwohner.

je 10,000 Einwohner der Städte (nach den Berichten der Medizinalverwaltung und nach WILEN).

Aus den Abbildungen wird ersichtlich, dass die Frequenzkurven der frischen Lues wellenförmig auf- und absteigen und dabei früher eine aufwärtsgerichtete, aber in den letzten Jahren eine sinkende Tendenz erkennen lassen. Ferner stellt man aus den Kurven fest, dass in den Städten verhältnässig mehr frische Lues als im ganzen Land und mithin auch in der Provinz zu konstatieren ist. Im ganzen Lande fand sie sich in den Jahren 1923—1938 zwischen etwa 4 und 6.5 ‰ von der Einwohnerzahl, während sie in Helsinki, Viipuri und Tampere hauptsächlich zwischen 10 und 50 ‰ lag. Bemerkenswert hoch stieg die Frequenzkurve der frischen Lues 1919 in Viipuri, der Hauptstadt der östlichsten Provinz, an.

### B. Formen.

In unserem Lande sind Berichte über Fälle der verschiedenen durch frische Lues verursachten Komplikationen veröffentlicht worden (HOLSTI, PIRILÄ).

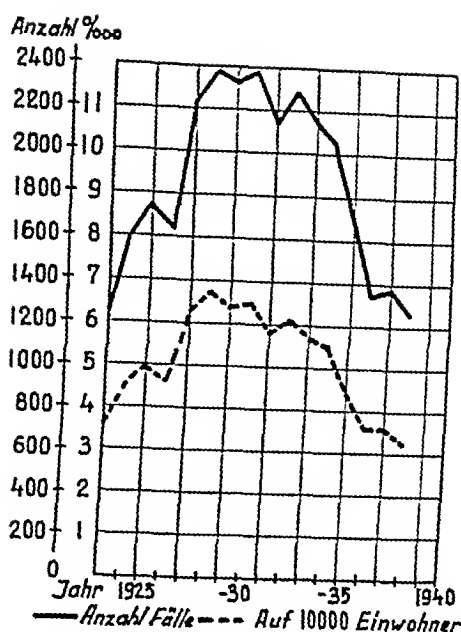


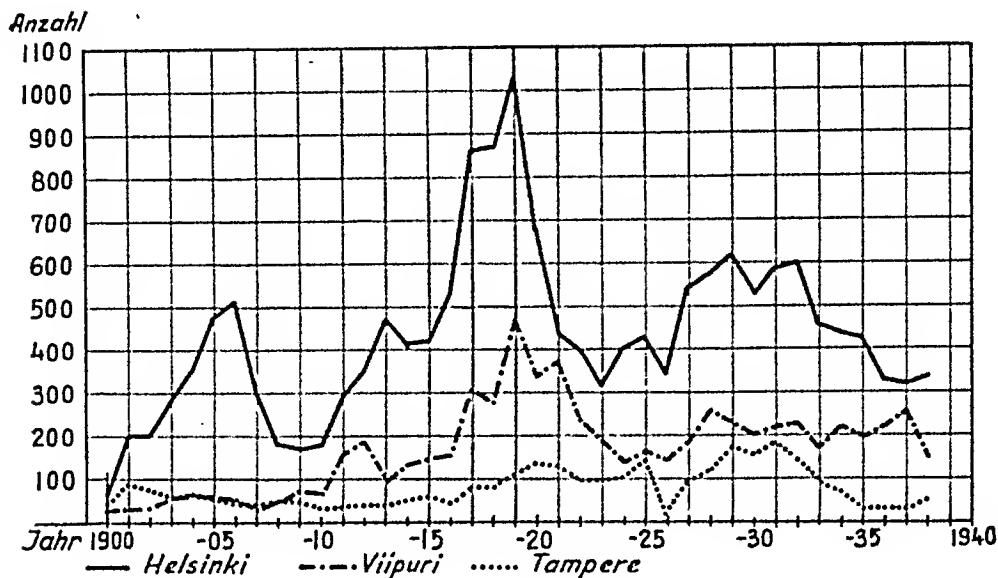
Abbildung 2. Die während der Jahre 1923—38 aus unserem ganzen Lande gemeldeten Fälle von frischer Lues und ihr Verhältnis je 10,000 Einwohner.

## Spätlues.

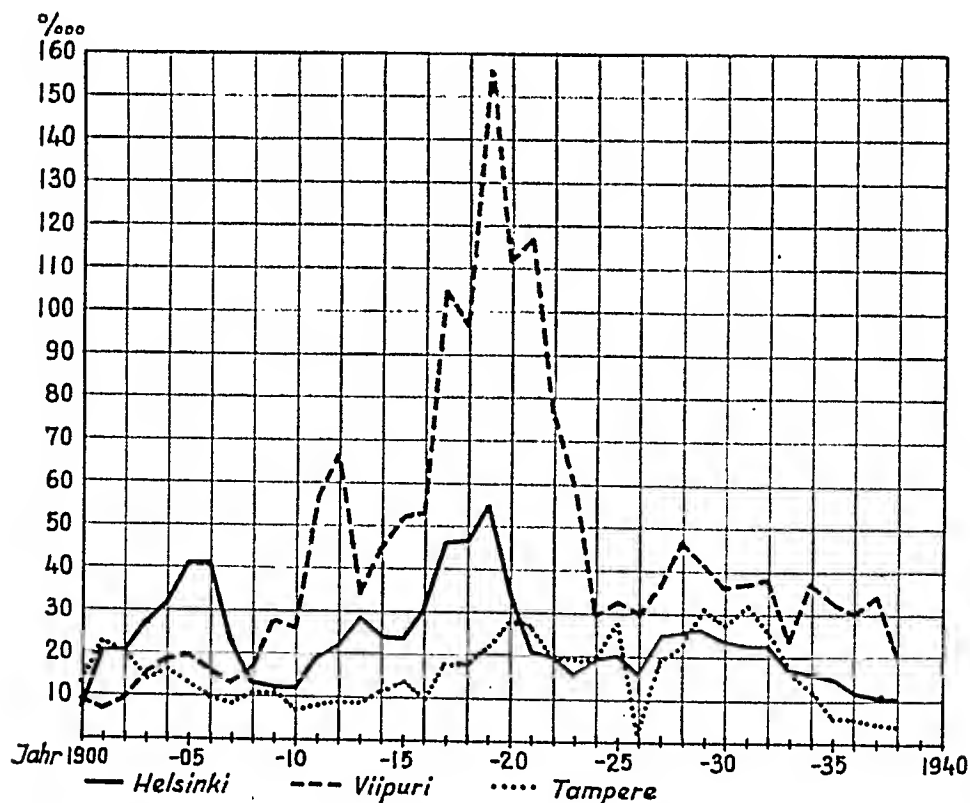
### A. Häufigkeit.

Die Angaben über die Häufigkeit der Spätlues (Lues III) in unserem Lande sind spärlich. Es liegt kein gutes einheitliches Bild über sie vor, weil die Fälle dieser Krankheit in den Rapporten der Kreisärzte an die Medizinalverwaltung nicht ausdrücklich angeführt werden. Auch andere Umstände tragen zu unserer diesbezüglichen beschränkten Kenntnis bei. Vor allem ist die Feststellung der latenten Luesfälle bei uns ungenügend betrieben.

Gewisse Aufschlüsse über die Frequenz der Spätlues in unserem Lande liefert uns jedoch die Zahl der Spätluespatienten, die in den venerischen Krankenhäusern in Behandlung gewesen sind. Abbildung 4 veranschaulicht die Zahl der während 1910—1938 alljährlich wegen Spätlues in die venerischen Krankenhäuser aufgenommenen Patienten wie auch ihr Verhältnis je 10,000 Bewohner des Landes.



A. Anzahl.



B. Verhältnis je 10,000 Einwohner.

Abbildung 3 A und B. Die während der Jahre 1900—38 aus drei Städten unseres Landes gemeldeten Fälle von frischer Lues.

Wie man sieht, lag die Menge der betreffenden Patienten, die alljährlich in die venerischen Krankenhäuser Aufnahme gefunden haben, im allgemeinen unter 1 ‰ von der ganzen Einwohnerzahl des Landes. Ebenso wie die Kurve für die wegen frischer Lues in die venerischen Krankenhäuser aufgenommenen Patienten

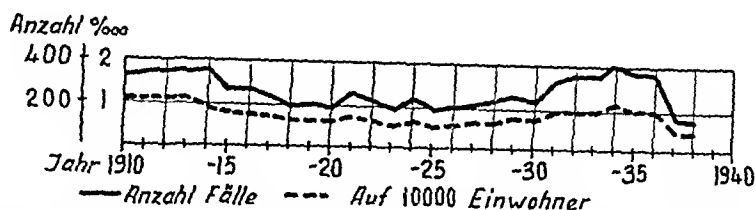


Abbildung 4. Die Gesamtzahl der während der Jahre 1910—38 wegen Spätlues in die venerischen Krankenhäuser unseres Landes aufgenommenen Patienten und ihr Verhältnis je 10,000 Einwohner.

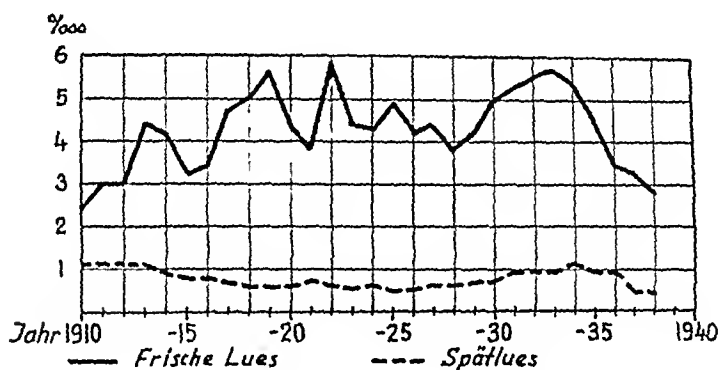


Abbildung 5. Die während der Jahre 1910—38 wegen frischer und Spätlues in die venerischen Krankenhäuser unseres Landes aufgenommenen Patienten, je 10,000 Einwohner berechnet. (Gegenseitiger Vergleich.)

schwankte, so bewegte sich auch die Kurve für die aufgenommenen Patienten mit Spätlues einigermassen auf und ab.

In Abbildung 5 habe ich die Zahl der während 1910—1938 wegen frischer Lues und wegen Spätlues in die venerischen Krankenhäuser des Landes aufgenommenen Patienten mit der Einwohnerzahl verglichen. Die Kurven scheinen nicht parallel zu laufen. Die für die frische Lues steigt bis zum Jahre 1922 an, umgekehrt sinkt aber die für die Spätlues von 1913 bis 1925, wonach sie erst aufwärts zu führen beginnt. Wahrscheinlich beruht dies auf

der Latenzzeit zwischen der frischen Lues und den spätluetischen Erkrankungen.

Aus den letzten Jahren haben wir ausserdem einige Untersuchungen über die Häufigkeit der Spätluës. Diese sind in Tabelle 1 zusammengestellt.

*Diese Untersuchungen, die an einer nicht ausgewählten Bevölkerung ausgeführt sind, lassen ahnen, dass die Lues in unserem Lande eine viel häufigere Krankheit ist, als man früher angenommen hat.*

Tabelle 1.

Untersucher	Untersuchungs-jahr	Untersuchungsort	Zahl der Untersuchten	Häufigkeit der Lues (Lues III) in %	Unspezifitäts-prozent (abzuziehen)
Turunen, A.	1935	I. Frauenklinik der Universität Helsinki, Schwangerenberatungsstelle	2390	3.8 (WR und KR)	0.75
Honkanen, A.	1936	Tub.-Krankenhaus in Helsinki	611	5.2 (KR)	0.66
Maijala, P.	1939	Eine Fabrik	527	1.3 (WR) 2.1 (KR) 2.8 (MBR II)	0.04 0.11 0.15

### B. Formen.

Im folgenden gebe ich eine Übersicht der in Finnland erschienenen Untersuchungen über die spätluetischen Erkrankungen:

Verfasser	Jahr	Gegenstand der Veröffentlichung
SOURANDER, J. ....	1840	Pathologie der Orchitis syphilitica
BONSDORFF, E. ....	1865	Syphilitische Gehirn- und Rückenmarkserkrankungen
GAHMBERG, F. ....	1868	Sarcocele syphilitica
HJELMMAN, J. ....	1890	Syphilitische Arthropathien
HJELMMAN, J. ....	1892	Über Gehirnsyphilis
STARCK, W. ....	1892	Behandlung der Tabes mit Jodkalium



Verfasser	Jahr	Gegenstand der Veröffentlichung
KROGIUS, A. ....	1893	Tabetische Gelenkaffektionen
HJELMMAN, J. ....	1894	Ein Fall von syphilitischer Pharynxstriktur
KARVONEN, J. ....	1894	Luetische Phlebitiden
COLLAN, V. ....	1895	Lebersyphilis
SUNDHOLM, A. ....	1895	Über tertiäre Rektalsyphilis
LYBECK, E. ....	1897	Ein durch Lues verursachter Fall von homonymer Hemianopsie
HOMÉN, E. ....	1899	Über Syphilis des Zentralnervensystems
KARVONEN, J. ....	1899	Nierensyphilome
RUNENENG, J. ....	1901	Ein Fall von syphilitischer Aortitis
" .....	1902	Ein Fall von Herzsyphilis
" .....	1902	Syphilitische Herzaffektionen
Sievers, R. ....	1902	Ein Fall von Herzsyphilis
" .....	1902	— — —
" .....	1902	Ein Fall von syphilitischer Aortitis
HOLSTI, H. ....	1903	Drei Fälle von luetischem Aortenaneurysma
HOMÉN, E. ....	1903	Ein Fall von arthropathischer Tabes
SIEVERS, R. ....	1903	Ein Fall von luetischer Aortitis
Tollet, A. ....	1903	Ein Fall von Pharynx- und Larynxsyphilis (Demonstration des Patienten)
Clopatt, A. ....	1904	Ein Fall von luetischer Osteitis
SIEVERS, R. ....	1904	Ein Fall von Herzsyphilis
" .....	1904	Ein Fall von syphilitischer Aortitis
" .....	1904	Ein Fall von Leber- und Herzsyphilis
HOMÉN, E. ....	1905	Ein Fall von Lues hereditaria tarda
KARVONEN, J. ....	1905	Drei Fälle von Dactylitis syphilitica
WINQVIST, G. ....	1910	Liquorveränderungen bei der Paralyse
HAGELSTAM, J. ....	1912	Ein Fall von Lebersyphilis
PETERSON, L. ....	1913	Ein Fall von syphilitischer Meningitis
PIPONIUS, H. ....	1913	Syphilitische innere Krankheiten
SJÖBLÖM, J. ....	1916	Aortenaneurysmen (teilweise syphilitische)
PIPONIUS, J. ....	1917	Ein Fall von auf hereditärer Basis entstandener Aortenlues
KERPPOLA, W. ....	1919	Ein Fall von luetischer Phlebitis
HAGELSTAM, J. ....	1921	Über Syphilis des Zentralnervensystems
TALLQVIST, T. ....	1921	Das klinische Bild der luetischen Leberkrankheiten
LEVANDER, Y. ....	1922	Ein Fall von Aortenaneurysma
JANSSON, G. ....	1922	Die Goldsol-Reaktion des Liquors bei Lues des Zentralnervensystems
PIRILÄ, P. ....	1923	Ein Fall von syphilitischer Polyarthrit
CEDERCREUTZ, A. ....	1925	Die Ursache der Hutchinsonson'schen Trias

Verfasser	Jahr	Gegenstand der Veröffentlichung
PIRILÄ, P. ....	1925	Ein Fall von Frühparalyse
HARLIN, O. ....	1930	Ein Fall von Meningitis heredosyphilitica
INGMAN, Å. ....	1930	Ein Fall vonluetischer Spondylitis
KERPPOLA, W. ....	1930	Blutdruck und Adrenalinreaktion bei Tabes dorsalis
ROTHSTRÖM, G. ....	1930	Die Frequenz der Paralyse in Helsinki
VESA, A. ....	1930	Vier möglicherweise durch Lues verursachte Fälle von Anämie mit hohem Index
SOINI, A. ....	1934	Der Anteil der Lues an der Entstehung von Herzfehlern
VANNAS, M. ....	1935	Durch Lues verursachte Blindheit
KERPPOLA, W. ....	1937	Leberlues
KAPLAN, J. ....	1938	Lungenlues
MAIJALA, P. ....	1938	Ein Fall, in dem Injektion von Histamin den Tod einesluetischen Koronarstenosepatienten verursacht hatte
TARKIAINEN, J. ....	1938	Ein Fall von rupturiertem,luetischem Aneurysma der Bauchorta (Dilatationsfall)
GORDIN, R. ....	1939	Aortenrupturen (teilweiseluetische)
MAIJALA, P. ....	1939	Ein Fall von Syphilis, die bis in die dritte Generation gewandert ist
KAUNISTO, N. ....	1940	Durch Lues verursachte Blindheit

Das grösste Interesse bietet unter diesen Veröffentlichungen meines Erachtens die Dissertation HJELLMAN's von 1892. Er hat die Journale der internmedizinischen, syphilitischen, chirurgischen und ophthalmologischen Abteilung des Allgemeinen Krankenhauses in Helsinki aus den Jahren 1878—1890 durchgesehen und so 1860 Fälle von tertiärer Syphilis zusammengestellt. In seinem Material kamen tertiäre Manifestationen in folgendem Verhältnis vor:

Affektionen der Haut .....	985 Fälle
, des Knochensystems .....	238 ,
, der Nasen- und Gaumenknochen .....	223 ,
, des Rachens und des weichen Gaumens .....	318 ,
, des Kehlkopfs und der Luftröhre .....	93 ,
, der Genitalorgane .....	50 ,
, der Hoden .....	32 ,

Affektionen verschiedener Schleimhäute .....	15 Fälle
• des Auges .....	32
• der Gelenke .....	10
• der Leber .....	32
Nervensyphilis { Gehirnsyphilis .....	218
{ Gehirn- und Rückenmarkssyphilis .....	12
{ Rückenmarkssyphilis .....	24
Verschiedene Affektionen .....	2

Hiernach ist in dem Material HJELLMAN's die Nervensyphilis durch etwa 14 % aller tertiären Fälle vertreten. Fälle von Aortensyphilis finden sich dagegen überhaupt nicht. Ihr Fehlen beruht wahrscheinlich darauf, dass die Aortensyphilis damals noch nicht bekannt war. Das auf sie bezügliche Problem begann sich ja erst um 1900 zu klären, als auch bei uns schon Runeberg (1901) einen Fall von syphilitischer Aortitis veröffentlichte. Runeberg behauptete auch in derselben Publikation, dass syphilitische Herzaaffektionen häufiger seien, als man angenommen habe, eine Auffassung, die sich später als richtig erwiesen hat.

### Die serologische Diagnostik der Lues in Finnland.

Die in Finnland gebräuchliche Modifikation der Wassermannschen Reaktion ist von STRENG und MURTO ausgearbeitet worden, die 1913 über sie berichteten. Im Laufe der Jahre hat diese Modifikation einige Abänderungen erfahren, und über ihre Resultate haben mehrere Autoren geschrieben: TIISALA und WEIJO (1914); MURTO (1916); NYSTÉN (1916); MURTO, PIRILÄ und HELME (1918); GRÖNROOS (1919); SNELLMAN (1924); SALMINEN (1928); STRENG, SIEVERS (OLOF) und VUORI (1933); OLIN (1935); TURUNEN (1935); AMINOFF (1939) und SIEVERS (1932, 1936, 1937, 1939 und 1941).

Die Kahnsche Ausflockungsreaktion und ihre Ergebnisse haben behandelt: SIEVERS (1932 und 1937); STRENG, SIEVERS und VUORI (1933); OLIN (1935) und HONKANEN (1936).

Über die Müllersche »Ballungsreaktion II« hat sich SIEVERS (1932 und 1937) geäußert.

## FRAGESTELLUNG.

Wie aus den obigen Ausführungen hervorgeht, liegen bei uns seit Anfang 1923 ziemlich gute Angaben über die Häufigkeit der frischen Lues vor. Es sind auch einige Arbeiten über die durch frische Lues verursachten Komplikationen veröffentlicht worden. Dagegen ist unsere Kenntnis über die Frequenz der Spätlues bei uns begrenzt. Desgleichen wissen wir wenig von der jetzigen Häufigkeit der verschiedenen Formen der Spätlues in den inneren Organen in unserem Lande. Es schien mir infolgedessen angebracht, folgende Fragen eingehender zu beleuchten:

1. *In welchem Masse kommt bei uns in Finnland seropositive Spätlues vor?*

2. *In welchem Umfang entwickeln sich in unbehandelten und mangelhaft behandelten Luesfällen Veränderungen in den inneren Organen und von welcher Art sind diese Veränderungen in Finnland?*

3. *Da in der Diagnostik der Lues heutzutage grossenteils empfindliche serologische Methoden zur Anwendung kommen, ist es meines Erachtens von Wichtigkeit, auch genauer festzustellen, inwieweit die gewöhnlichsten in Finnland gebräuchlichen serologischen Reaktionen der Lues zuverlässig sind.*

## Material und Methodik.

An der medizinischen Poliklinik des Allgemeinen Krankenhauses (Universitätskliniken) in Helsinki war es bis Mitte 1935 üblich, die Wassermannsche Reaktion nur dann festzustellen, wenn »die klinischen Symptome auf das Vorhandensein von Lues hinwiesen«. Der Chef der Anstalt, Professor ÖSTEN HOLSTI, führte jedoch damals eine Änderung in dieser Beziehung durch, und

danach hat die Prüfung der Luesreaktionen systematisch bei allen Patienten stattgefunden.

In der Zeit vom 1. 1. 1936 bis zum 31. 12. 1937 wurde die medizinische Poliklinik von 10,954 Patienten besucht. Ihre Blutproben wurden parallel auf vier Luesreaktionen hin untersucht, und zwar auf die Modifikation der gewöhnlichen in Finnland gebräuchlichen Wassermannreaktion ohne Cholesterinzusatz (WR I), die Modifikation der durch Cholesterinzusatz sensibilisierten Wassermannreaktion (WR II), die Kahnsche Ausflockungsreaktion (KR) und die Müllersche »Ballungsreaktion II« (MBR II). Mit der Anwendung der zuletzt genannten Reaktion wurde nicht von Anfang 1936 an, sondern erst etwa  $\frac{1}{2}$  Jahr später begonnen. Ausserdem waren einige Blutproben so gering, dass das Serum nicht zur Prüfung aller vier in Rede stehenden Reaktionen ausreichte. So wurden WR I und WR II bei den Blutproben von 10,953, KR bei denen von 10,925 und MBR II bei denen von 7,841 Patienten benutzt. Die Ausführung der Reaktionen fand im Serobakteriologischen Institut der Universität Helsinki (Vorstand: Prof. Dr. med. Osv. RENKONEN) statt. Sie wurde fast durchgehend von Doz. Dr. med. OLOF SIEVERS vorgenommen. Die genauere Technik der Reaktionen wird ersichtlich aus Sievers' Arbeiten von 1932 (Acta Soc. Med. fenn. Duodecim, Ser. A, Tom. XV, Fasc. 21) und 1937 (Acta path. et microbiol. scand. (Dän.) 14, Fasc. 3 und Finska Läk. sällsk. Hdl. 80, 395, 534 und 573).

Das Ergebnis war, dass bei 387 aller untersuchten Patienten mindestens eine der genannten Luesreaktionen positiv (+) war. Ausserdem war die Reaktion bei 14 suspekt (+?,  $\pm$ , -?).

Es war nun meine Absicht, für eine gründlichere Untersuchung alle Patienten, bei denen auch nur eine Luesreaktion positiv oder suspekt gewesen war, in die Poliklinik zurückzubekommen, also  $387 + 14 = 401$  Patienten. Zu diesem Zweck richtete ich an die Patienten einen Brief, in dem ich sie bat, sich wieder in der medizinischen Poliklinik einzufinden. Der Brief hatte folgenden Wortlaut: »Da aus unseren Untersuchungen hervorgeht, dass Ihr Blut nicht gesund ist, ist es für Sie ausserordentlich wichtig, das Sie möglichst umgehend für eine genauere Untersuchung wieder in die medizinische Poliklinik kommen.

Paavo Maijala.  
Arzt.»

Zu der Kontrolluntersuchung stellten sich jedoch nur 236 Patienten (59 %) ein. Von den ausgebliebenen Patienten waren einige zu Hause gestorben, andere wohnten weit weg, weshalb sie nicht kommen konnten; warum aber die übrigen trotz erneuter Aufforderung nicht erschienen, ist schwer zu sagen. Bemerkenswert ist, dass der grösste Teil der Ausgebliebenen auf die erste Halbjahresperiode meiner Untersuchung entfiel. Danach leisteten viel weniger der Aufforderung zu der Kontrolluntersuchung keine Folge.

Sämtliche 401 Fälle ziehe ich bei der Behandlung der Frage von der Frequenz der Lues heran. Die zur Kontrolluntersuchung eingetroffenen 236 Fälle berücksichtige ich andererseits bei der Erörterung der Frage nach der Spezifität der serologischen Luesreaktionen. Von den in diesen Kontrollfällen enthaltenen 180 sicheren + 19 wahrscheinlich sicheren Spätluesfällen mache ich schliesslich im Zusammenhang mit der Organluesfrage Gebrauch.

Bei der Behandlung der Luesfrequenz gehe ich davon aus, dass die Spezifität der serologischen Luesreaktionen für alle 401 Fälle dieselbe wie für die zur Kontrolluntersuchung erschienenen 236 Patienten ist.

Die zur Kontrolluntersuchung gekommenen 236<sup>1</sup> Patienten habe ich selbst untersucht und dabei folgendes Verfahren angewandt:

Die Anamnese nahm ich von jedem Patienten auf. Ich fragte genau, wann und an welchen Geschlechtskrankheiten der Patient erkrankt war und was für Therapie er erhalten hatte, falls es sich bei ihm um Lues handelte. Wenn der Patient am Penis ein Geschwür aufgewiesen hat, das der Arzt oder der Patient, ohne einen Arzt aufzusuchen, für einen weichen Schanker gehalten hat, habe ich in der Anamnese »Ulcus molle« notiert.

Die klinische Untersuchung habe ich gleichfalls selber ausgeführt. Dazu gehörten folgende Spezialuntersuchungen:

Eine Röntgenuntersuchung des Thorax.

Ein Elektrokardiogramm.

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<sup>1</sup> Die vollständige, finnisch abgefasste Kasuistik wird in der medizinischen Poliklinik des Allgemeinen Krankenhauses in Helsinki aufbewahrt und kann dort eingesehen werden.

Eine Untersuchung der Lumbalflüssigkeit.  
Die Senkungsreaktion des Blutes.  
Das Blutbild.

Ausserdem wurden bei jedem Patienten die Luesreaktionen erneut geprüft.

Bei Bedarf wurden noch einige andere Untersuchungen vorgenommen. So erfolgten in einem Teil der Fälle eine Prüfung der Augen und der Augenhintergründe, eine Röntgenaufnahme des Schädels, eine oto-, rhino- und laryngologische Untersuchung usw. Zu Beginn meiner Arbeit beabsichtigte ich, wenigstens bei allen über Bauchbeschwerden klagenden Patienten eine Röntgenuntersuchung des Magens durchzuführen, aber aus pekuniären Gründen war dies zu meinem grossen Bedauern nicht möglich.

In den verschiedenen Kapiteln werde ich noch genauer auf die jeweils in Betracht kommende Untersuchungsmethodik eingehen.

## EIGENE UNTERSUCHUNGEN.

### Die Häufigkeit der Spätlues.

Die Häufigkeit der seropositiven Spätlues bei den Patienten der medizinischen Poliklinik des Allgemeinen Krankenhauses in Helsinki während der Jahre 1936—1937.

Die Häufigkeit der seropositiven Lues aller Grade bei den Patienten der medizinischen Poliklinik wird aus den Tabellen 2 und 3 ersichtlich. Ausserdem lassen diese die Frequenz der serosuspekten Lues erkennen. Tabelle 2 gibt Aufschluss über die Untersuchungsergebnisse der verschiedenen Luesreaktionen. Damit diese Ergebnisse die Häufigkeit der Lues und nicht nur die der positiven und suspekten Reaktionen zum Ausdruck bringen, habe ich von ihnen das für jede Reaktion gefundene Unspezifitätsprozent (darüber genauer in dem Kapitel über die Spezifität der serologischen Luesreaktionen) abgezogen. So ergibt sich für die WR I-positive und -suspekte Lues aller Grade insgesamt 2.5 %, für die WR II-positive und -suspekte 2.78 %, für die KR-positive und -suspekte 3.28 % und für die MBR II-positive und -suspekte 3.1 %.

Tabelle 2.

Die Häufigkeit der seropositiven und -suspekten Lues bei den Patienten der medizinischen Poliklinik in den Jahren 1936—1937<sup>1</sup>.

Reaktion	Gesamtzahl der Untersuchten	Positiv (+)		Suspekt (+?)		Suspekt ( $\pm$ , —?)		Zusammen %
		Anzahl	%	Anzahl	%	Anzahl	%	
WR I . . . . .	10,953	219	2.00—0.04 = 1.96	3	0.03—0.03 = 0	62	0.57—0.03 = 0.51	2.50
WR II . . . . .	10,953	250	2.28—0.06 = 2.22	2	0.02—0.01 = 0.01	62	0.56—0.01 = 0.55	2.78
KR . . . . .	10,925	364	3.33—0.11 = 3.22	2	0.02—0.01 = 0.01	6	0.06—0.01 = 0.05	3.28
MBR II . . . . .	7,841	243	3.10—0.15 = 2.95	12	0.15—0.07 = 0.08	11	0.14—0.07 = 0.07	3.10

<sup>1</sup> Die klein gedruckten Zahlen geben die Unspezifitätsprozente der Reaktionen an.



Tabelle 3.

Mindestens eine der vier geprüften Luesreaktionen positiv oder suspekt<sup>1</sup>.

Gesamtzahl der Unter- suchten	Positiv (+)		Suspekt (+?, ±, —?)		Zu- sammen %
	Anzahl	%	Anzahl	%	
10,954	387	$3.53 - 0.15 = 3.38$	14	$0.13 - 0.07 = 0.06$	3.44

In Tabelle 3 habe ich die Häufigkeit der Lues so berechnet, dass ich alle Fälle berücksichtigte, in denen zum mindesten eine der genannten vier Luesreaktionen positiv oder suspekt war. Auf diese Weise habe ich in meinem Material als Häufigkeitsprozent der Lues aller Grade 3.44 erhalten.

Von der seropositiven Lues meines Materials sind 90 % Spät-lues, 4 % frische Lues und 6 % kongenitale Lues. Zieht man dies in Betracht, so errechnet man, dass von den Patienten der medizinischen Poliklinik an WR I-positiver und -suspekter Spätlues insgesamt 2.25 %, an WR II-positiver und -suspekter 2.5 %, an KR-positiver und -suspekter 2.95 % und an MBR II-positiver und -suspekter 2.79 % leiden.

Im vorliegenden Material ist das Häufigkeitsprozent der Lues mithin ziemlich hoch. Das erklärt sich teilweise daraus, dass das Material von kranken Personen gebildet wird. In meiner früheren Untersuchung, die subjektiv gesunde Personen betraf, war das Häufigkeitsprozent der Lues etwas niedriger (Tabelle 4).

Zum Vergleich habe ich in Tabelle 4 alle in Finnland und einige im Ausland erschienene Angaben über die Frequenz der Lues zusammengestellt. Dazu kann ich erwähnen, dass Prof. Ö. Ho'sti in den Jahren 1938—39 am Serobakteriologischen Institut der Universität Helsinki bei allen seinen 531 Privatpatienten die WR und KR hat feststellen lassen. Dabei war WR in 2.1 % und KR in 2.8 % positiv.

In Schweden und Deutschland ist in den letzten Jahren bedeutend weniger Lues als bei uns vorgekommen. Ebenso verhält es sich in Dänemark wenigstens bezüglich der frischen Lues (Lomhold 1935). Dies beruht auf der energischen Luesbekämpfung,

<sup>1</sup> Die klein gedruckten Zahlen geben die Unspezifitätsprozente der Reaktionen an.

**Tabelle 4.**  
Die Häufigkeit der Lues in einigen Ländern.

Autor	Land	Jahr	Umfang des Ma- terials	Art des Materials	Häufigkeit der Lues
GULDBERG, G.	Norwegen	1932	8,235	Obduktionsfälle	5.8 % (bei der Obduk- tion Zeichen von Lues)
ELDH, S. ....	Schweden	1926—31	17,108	Pat. eines Krankenh. für innere Med.	2.2 % (WR)
KALLNER, S. ..	Schweden	1939	7,750	Pat. einer Poliklinik f. innere Krankh.	0.66 % (WR, KR und MBR)
MELCHOR, L. ..	Dänemark	1914—1920	4,717	Obduktionsfälle, klin. Fälle	7.6 % (WR, klinisch, bei der Obduktion)
LANGER, E. ..	Deutschland	1906—1925	23,015	Obduktionsfälle	5.5 % (bei der Obduk- tion Zeichen von Lues)
Nickel, H. . .	Deutschland	1907—1933	11,476	Obduktionsfälle	7.2 % (bei der Obduk- tion Zeichen von Lues)
ROMBERG, E. ..	Deutschland	1918	6,850	Pat. eines Krankenh. f. innere Med.	10.1 %
STRELOW, K. ..	Deutschland	1921—1925	14,941	Obduktionsfälle	7.4 % (bei der Obduk- tion Zeichen von Lues)
JÜLLER, R. ..	Deutschland	1938	125,000	Massenuntersuchung	0.8 % (Chediak)
HINTON, W. ..	U.S.A.	1915—1919	10,427	Schwangere	4.2 % + suspekt 3.9 % (WR)
MELSON, N. ..	U.S.A.	1930—1934	17,624	Schwangere	1.5 % + suspekt 1.1 % (WR)
SONDERLEHR, R. et al.	U.S.A.	1936	1,782	Männl. Neger	26.5 % (KR und Kol- mersche Reaktion)
Conference on syphilis ....	U.S.A.	1937			5 à 10 % (Lues aller Stadien zusammen)
McDANIEL, J.	U.S.A.	1937	6,911		18.9 (serologisch) Weiss. Neger { Männer 33.8 % Frauen 34.5 % Männer 7.1 % Frauen 7.3 % }
ELL, E. ....	U.S.A.	1938	27,872	Obduktionsfälle	2.77 % (bei der Obduk- tion Zeichen von Lues)
Emmie, Ch. ..	Südamerika Rio de Janeiro	1936			ca. 35 %
URUNEN, A.	Finnland	1935	2,390	Pat. der Schwangeren- beratungsstelle der Frauenklinik	3.8 % (WR und KR)
ONKANEN, A.	Finnland	1936	611	Pat. des Tnb.-Kran- kenhauses	5.2 % (KR)
AIJALA, P. ..	Finnland	1939	527	Subjektiv gesunde Fabrikarbeiter	{ 1.3 % (WR) 2.1 % (KR) 2.8 % (MBR II)
AIJALA, P. ..	Finnland	1942	10,954	Pat. einer medizini- schen Poliklinik	{ 2.5 % (WR I) 2.78 % (WR II) 3.28 % (KR) 3.1 % (MBR II)

die in diesen Ländern während der letzten Zeit ausgeführt worden ist. Dagegen findet man sowohl in den Vereinigten Staaten von Nordamerika als in Südamerika mehr Lues als bei uns. Ausserdem ist die Lues in den Vereinigten Staaten unter der Negerbevölkerung mehr verbreitet.

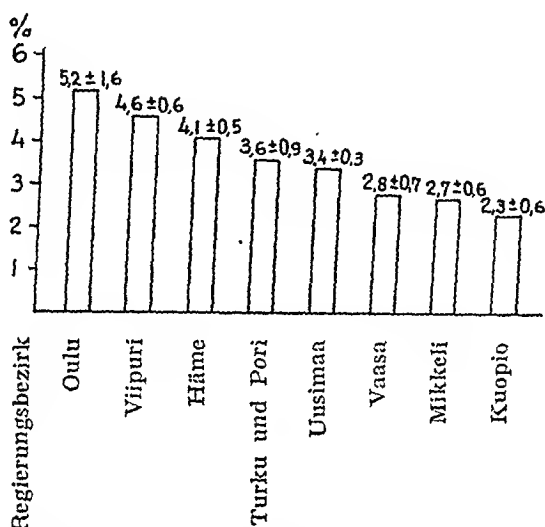


Abbildung 6. Die Häufigkeit der Lues nach den verschiedenen Regierungsbezirken.

#### *Die Häufigkeit der Lues nach den verschiedenen Regierungsbezirken.*

Aus Abbildung 6 ist zu ersehen, in welcher Menge Lues nach meinem Material bei den aus verschiedenen Regierungsbezirken stammenden Patienten vorkommt (von den Hundertsätzen habe ich das Unspezifitätsprozent der Reaktionen abgezogen). Die Tabelle lässt erkennen, dass die Lues am stärksten bei den Patienten aus dem Regierungsbezirk Oulu und danach bei denen aus den Regierungsbezirken Viipuri und Häme vertreten ist. Jedoch sind die Differenzen so klein, dass mathematisch betrachtet kein sicherer Unterschied vorhanden ist.

#### *Das Vorkommen der Lues nach dem Alter und dem Geschlecht.*

Um in Erfahrung zu bringen, in welcher Altersperiode seropositive und -suspekte Lues am meisten und für welches Geschlecht sie in grösserer Menge anzutreffen ist, habe ich mein

Material nach dem Alter und dem Geschlecht gruppiert. Da die MBR II bei weitem nicht in allen Fällen festgestellt worden ist, habe ich keine Gruppierung der Befunde vorgenommen.

Tabelle 5.

Die WR I-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert <sup>1</sup>.

Reaktion	Alter Jahre	Geschlecht	Zahl der Untersuchten	Positiv (+) %	Suspekt (+?, ±, —?) %	Zusammen %
WR I	unter 20	♂	320	0,27	0,28	0,55
„	20—30	♂	1,147	2,05	0,23	2,28
„	31—40	♂	996	2,77	1,37	4,14
„	41—50	♂	739	4,56	0,65	5,21
„	51—60	♂	684	2,15	0,99	3,14
„	über 60	♂	656	1,03	—	1,03
„	unbekannt	♂	110	0,87	—	0,87
WR I	Summe	♂	4,652	2,33	0,60	2,93
WR I	unter 20	♀	574	1,35	—	1,35
„	20—30	♀	1,485	1,37	0,44	1,81
„	31—40	♀	1,436	1,77	0,86	2,63
„	41—50	♀	967	1,82	0,38	2,20
„	51—60	♀	970	2,43	0,69	3,12
„	über 60	♀	759	1,41	0,49	1,90
„	unbekannt	♀	110	0,87	—	0,87
WR I	Summe	♀	6,301	1,69	0,51	2,20

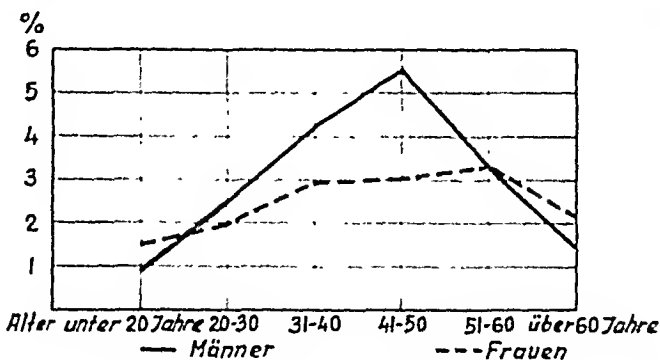


Abbildung 7. Die WR I-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert <sup>1</sup>.

<sup>1</sup> Das Unspezifitätsprozent abgezogen.

Die Ergebnisse finden sich für WR I in Tabelle 5 und Abbildung 7, für WR II in Tabelle 6 und Abbildung 8 und für KR in Tabelle 7 und Abbildung 9.

Tabelle 6.

Die WR II-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert <sup>1</sup>.

Reaktion	Alter Jahre	Geschlecht	Zahl der Untersuchten	Positiv (+) %	Suspekt (+?, ±, —?) %	Zusammen %
WR II	unter 20	♂	320	0.88	—	0.88
»	20—30	♂	1,147	2.12	0.34	2.46
»	31—40	♂	996	2.95	1.29	4.24
»	41—50	♂	739	4.81	0.67	5.48
»	51—60	♂	684	2.14	1.16	3.30
»	über 60	♂	656	1.01	0.45	1.46
»	unbekannt	♂	110	1.76	—	1.76
WR II	Summe	♂	4,652	2.48	0.70	3.18
WR II	unter 20	♀	574	1.51	—	1.51
»	20—30	♀	1,485	1.62	0.33	1.95
»	31—40	♀	1,436	2.24	0.69	2.93
»	41—50	♀	967	2.32	0.71	3.03
»	51—60	♀	970	2.83	0.51	3.34
»	über 60	♀	759	1.70	0.51	2.21
»	unbekannt	♀	110	0.85	—	0.85
WR II	Summe	♀	6,301	2.03	0.48	2.51

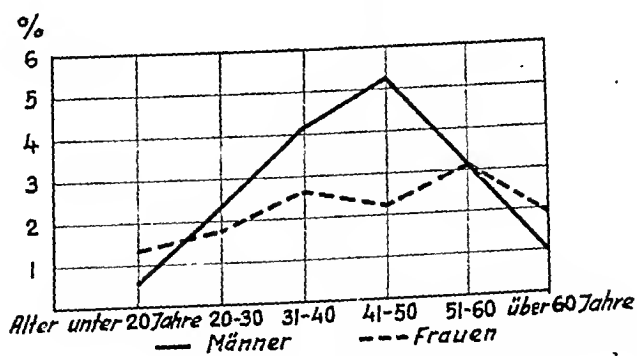


Abbildung 8. Die WR II-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert <sup>1</sup>.

<sup>1</sup> Das Unspezifitätsprozent abgezogen.

Tabelle 7.

Die KR-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert<sup>1</sup>.

Reaktion	Alter Jahre	Geschlecht	Zahl der Untersuchten	Positiv (+) %	Suspekt (+?, ±, -?) %	Zusammen %
KR	unter 20	♂	318	1.78	—	1.78
•	20—30	♂	1,146	2.68	0.08	2.76
•	31—40	♂	995	4.92	0.09	5.01
•	41—50	♂	736	5.87	—	5.87
•	51—60	♂	680	4.45	—	4.45
•	über 60	♂	655	1.72	—	1.72
•	unbekannt	♂	169	1.72	—	1.72
KR	Summe	♂	4,639	3.71	0.04	3.75
KR	unter 20	♀	574	1.46	0.16	1.62
•	20—30	♀	1,482	1.98	0.06	2.04
•	31—40	♀	1,432	3.17	0.13	3.30
•	41—50	♀	965	4.14	—	4.14
•	51—60	♀	968	3.71	0.09	3.80
•	über 60	♀	756	2.54	0.12	2.66
•	unbekannt	♀	109	1.72	—	1.72
KR	Summe	♀	6,286	2.85	0.09	2.94

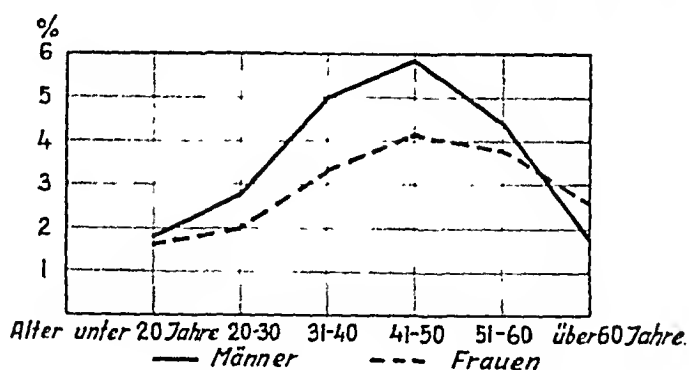


Abbildung 9. Die KR-positiven und -suspekten Luesfälle, nach dem Alter und Geschlecht gruppiert<sup>1</sup>.

Man konstatiert, dass bei den Männern am meisten seropositive Lues in der Altersperiode von 41 bis 50 Jahren auftritt. Da findet man bei ihnen WR I-positive Lues in 5.21 %, WR II-posi-

<sup>1</sup> Das Unspezifitätsprozent abgezogen.

live in 5.48 % und KR-positive 5.87 %. Die Frauen zeigen am meisten WR I- und WR II-positive Lues in der Altersklasse von 51 bis 60 Jahren und KR-positive in der Altersklasse von 41 bis 50 Jahren. Alsdann ist bei ihnen WR I-positive Lues in 3.12 %, WR II-positive in 3.34 % und KR-positive in 4.14 % festzustellen.

In meinem ganzen Material findet sich *Lues bei den Männern etwa 1.3 mal mehr als bei den Frauen.*

In meiner kleinen früheren Arbeit war Lues am meisten bei den Männern der Altersklasse von 31 bis 40 Jahren und bei den Frauen der Altersklasse von 20 bis 30 Jahren, d. h. also bei jüngeren Individuen als in der vorliegenden Untersuchung anzutreffen. Dieser Unterschied beruht darauf, dass meine frühere Arbeit subjektiv gesunde Personen umfasste, bei denen sich die spätluetischen Affektionen noch nicht entwickelt hatten. Das Objekt der jetzigen Untersuchung haben dagegen zum grössten Teil solche gebildet, bei denen die spätluetischen Erkrankungen bereits ausgeprägt waren.

Tabelle 8 veranschaulicht das Verhältnis der Lues bei den Männern und Frauen in einigen Ländern.

**Tabelle 8.**

Das Verhältnis der Lues bei Männern und Frauen in einigen Ländern.

Autor	Land	Jahr	Verhältnis Männer : Frauen
LANGEN, E. ....	Deutschland	1906—25	1,6 : 1
NICKEL, H. ....	Deutschland	1907—33	2,2 : 1
GÜRICH ....	Deutschland	1914—24	2,2 : 1
STIELOW, K. ....	Deutschland	1921—25	1,1 : 1
MAYNARD, JR. et al. ....	U.S.A.	1935	2,0 : 1
MCDANIEL, J. G. ....	U.S.A.	1937	0,97 : 1
KALLNER, SIXTEN ....	Schweden	1939	1,2 : 1
MAIJALA, P. ....	Finnland	1942	1,3 : 1

### *Die ihrer Krankheit Bewussten und Unbewussten.*

In welchem Umfang die Luetiker laut Angabe ihrer Krankheit bewusst gewesen sind, erhellt aus Tabelle 9. Wir sehen, dass *die männlichen Luetiker in 34.2 % zugaben, dass sie von ihrer Krank-*

heit wussten, die weiblichen in 26.4 %. Die Männer haben dieses Verhalten ungefähr 1.3 mal häufiger eingestanden als die Frauen. Ferner zeigt es sich, dass bei 20.2 % der männlichen und bei 70.8 % der weiblichen Luetiker in der Anamnese keine venerischen Krankheiten erwähnt waren. Die einschlägigen Daten einiger ausländischen Forscher, die aus Tabelle 9 ersichtlich werden, bewegen sich in derselben Richtung wie meine Resultate.

**Tabelle 9.**  
Ihrer Lues Bewusste und Unbewusste.

	Menge	In der Anamnese							
		Lues		Keine Lues		Eine vener. Krankheit		Keine vener. Krankheiten	
		Zahl	%	Zahl	%	Zahl	%	Zahl	%
Männliche Luetiker	114	39	34.2	75	65.8	91	79.8	23	20.2
Weibliche Luetiker	106	28	26.4	78	73.6	31	29.2	75	70.8
Zusammen	220	67	30.5	153	69.5	122	55.5	98	44.5

**Tabelle 10.**  
Bekanntschaft der Patienten mit ihrer Lues. Vergleich der Ergebnisse einiger Autoren.

Autor	Land	Jahr	Ihrer Lues Bewusste		
			Männer %	Frauen %	Männer + Frauen %
ROMBERG, E. ....	Deutschland	1918	40	18	
V. JAGIĆ u. ZIMMERMANN-MEINZINGEN .....	Deutschland	1937			25
MAYNARD, JR. et al. ....	U.S.A.	1935			55
MOORE, J. E. ....	U.S.A.	1936	75	67	
MAIJALA, P. ....	Finnland	1942	34.2	26.4	30.5

»Omnis syphiliticus mendax« ist ein alter Spruch, der im grossen und ganzen noch heute gilt. Man darf behaupten, dass auch meine Lueskranken die Wahrheit verheimlicht haben, woraus sich die geringe Zahl der mit ihrer Lues Bekannten erklärt. Es



ist auch vorgekommen, dass die Patienten anfangs das Wissen um ihre Krankheit leugneten, aber nach mehreren Besuchen und infolgedessen gewissermassen bei näherer Bekanntschaft mit mir auf erneute Befragung erklärten, dass sie sich ihrer Lues bewusst gewesen seien. Aus diesem Grunde halte ich es für möglich, dass meine Ergebnisse in grossen Zügen der Wahrheit entsprechen.

Meine Resultate bestätigen die Auffassung, dass die primären und sekundären Symptome sich in einem erheblichen Teil der Luesfälle nicht entwickeln oder so unbedeutend bleiben, dass sie nicht wahrzunehmen sind.

## Die Formen der Spätluës.

### Die kardiovaskulären Veränderungen.

#### I. Methodik.

Im Gegensatz zu der Diagnose des kompliziertenluetischen Aortenprozesses ist die des unkomplizierten schwierig, und dabei ist keine Methode allein zutreffend. Um eine frühe kardiovaskuläre Lues festzustellen, sind daher mehrere Untersuchungen erforderlich. Aus diesem Grunde habe ich die gewöhnliche physikalische und elektrokardiographische Untersuchung durch verschiedenartige röntgenologische Verfahren ergänzt.

Die von mir angewandten röntgenologischen Methoden sind folgende:

1. Die Bestimmung der Grösse des transversalen Durchmessers des Aortenbogens.

2. Die Bestimmung der Breite der Aorta ascendens.

3. Die Bestimmung des Kreuzfuchs-Masses.

4. Die Bestimmung der Höhe der Aorta.

5. Abgesehen von diesen Untersuchungen zur Feststellung der Vergrösserung der Aorta habe ich die Grösse des Herzens bestimmt, obgleich dieselbe bei der Diagnose der Aortenprozesse nicht von Bedeutung ist.

Die Zunahme der Dichte und die Veränderung der Pulsation

in der Aorta habe ich nicht berücksichtigt, weil sie der Subjektivität einen zu weiten Spielraum gewähren.

Bei der Aufnahme der Röntgenbilder standen die Patienten in einem Fokus-Filmabstand von 150 cm, und die Bilder sind bei »mittlerer Atemstellung« aufgenommen.

### 1. Die Grösse des transversalen Durchmessers des Aortenbogens.

Wenn das Bild in antero-posteriorer Richtung aufgenommen wird, findet man nicht direkt die Breite der Aorta, sondern die Grösse ihres transversalen Durchmessers: die grössten Abstände des rechten und linken Randes des Aortenbogens von der Medio-sternallinie aus zusammengerechnet, die Semidiameter (VAQUEZ-BORDET).

In Ermangelung eines eigenen Normalmaterials habe ich mich bei der Beurteilung der Grösse des transversalen Durchmessers des Aortenbogens auf das anscheinend gute Material von KEMP und COCHEMS (1937) gestützt. Diese Forscher haben teleröntgenologisch nach VAQUEZ-BORDET die Länge des transversalen Durchmessers des Aortenbogens bei 1,000 syphilitischen und 600 nicht-syphilitischen Personen bestimmt. Ihr Material gruppieren sie nach dem Geschlecht und Alter und ausserdem nach folgenden Gesichtspunkten:

1. Personen, die keine Herzkrankheit hatten.
2. Personen, die eine nichtsyphilitische Herzkrankheit (meist Hypertonie+Arteriosklerose) hatten.
3. Personen, die eine unkomplizierte oder komplizierte syphilitische Herzkrankheit hatten.

Die Masse, die sie für den transversalen Durchmesser des Aortenbogens angeben, sind folgende:

Geschlecht	Alter Jahre	Äusserste Schwankungen der Weite des Aortenbogens, cm		
		Keine Herzaffektion	Nicht-syphilitische Herzaffektion	Komplizierte oder unkomplizierte syphilitische Herzaffektion
♂	0—19	4.7—5.8	5.5—5.5	—
		4.1—6.2	5.4—5.4	—
	20—29	4.1—7.3	5.2—7.2	—
		4.5—7.5	4.8—6.3	5.7—7.5
	30—39	4.5—7.0	6.2—7.6	—
		4.5—7.1	5.5—7.2	6.0—8.6
	40—49	5.2—7.6	6.3—9.8	—
		4.8—7.6	5.3—7.9	5.5—13.0
	50+	5.5—6.8	6.2—9.7	—
		5.2—7.0	5.3—9.4	5.5—13.0
♀	0—19	4.2—5.8	4.5—5.0	—
		4.7—5.1	—	—
	20—29	4.2—5.9	4.4—4.5	—
		3.9—6.0	3.9—7.6	—
	30—39	3.9—7.0	5.0—8.0	—
		4.3—6.6	5.0—6.9	6.2—7.5
	40—49	5.2—6.4	5.6—7.5	—
		4.8—6.6	5.6—7.9	5.9—8.3
	50+	5.5—6.1	5.8—8.0	—
		5.2—6.2	6.0—7.1	6.0—8.8

(Nach KEMP und COCHEMS.)

## 2. Die Breite der Aorta ascendens.

Die Breite der Aorta kann man unmittelbar in Seitenbildern zum Vorschein bringen. Bei der Aufnahme der Seitenbilder habe ich die Patienten — bei noch völlig freiem Mittelfeld — gedreht, bis die Aorta in ihrer kleinsten Breite scharf zu sehen war. Die Seitenbilder können aufgenommen werden, indem man den Patienten nach links (erste Schrägrichtung oder Fechterstellung) oder nach rechts (zweite Schrägrichtung oder Boxerstellung) wendet. Die zweite Schrägrichtung gilt im allgemeinen als empfehlenswerter, weil die anderen Organe des Thorax dabei nicht so

sehr stören wie bei der Untersuchung in der ersten Schrägrichtung (ASSMANN, ALWENS). Nach REICH (1926) ist die Breite der Aorta ascendens auf Bildern, die in der I. und II. Schrägstellung aufgenommen sind, in 70 % die gleiche.

Ich habe mich bei der Bestimmung der Breite der normalen Aorta ascendens auf LIPPMANN und QUIRING gestützt. Nach ihnen übersteigt die Breite der Aorta ascendens in der I. Schrägrichtung auf dem bei dem Fokus-Filmabstand 150 cm aufgenommenen Bild gewöhnlich nicht 3.5 cm. Das zunehmende Alter wirkt nach ihnen nicht stark auf die Verbreiterung der Aorta ein.

### 3. *Das Kreuzfuchs-Mass.*

KREUZFUCHS (1920) lässt den Patienten dicken Kontrastbrei verschlingen, und das Bild wird in antero-posteriorer Richtung aufgenommen, wobei das von dem nach links führenden Aortenbogen hervorgerufene meniskusförmige sogenannte »Aortenbett des Ösophagus« zum Vorschein kommt. Er misst den Abstand zwischen dem tiefsten Punkt des Aortenbetts des Ösophagus und dem äussersten linken Rand des Aortenschattens. So ergibt sich das Mass des Isthmus aortae unmittelbar oberhalb des Punktes, wo der Arcus aortae in die Aorta ascendens übergeht.

Nach WEISS und LAUDA (1921) überschreitet das Kreuzfuchs-Mass in dem orthodiographisch aufgenommenen Bild nicht 2.6 cm.

Ich habe als obere Grenze des normalen Kreuzfuchs-Masses 2.8 cm betrachtet, d. h. das Mass, welches man erhält, wenn das orthodiographische Mass von WEISS und LAUDA mathematisch dem Fokus-Filmabstand 150 cm entsprechend umgewandelt wird.

### 4. *Die Höhe der Aorta.*

Unter der Höhe der Aorta wird die Strecke verstanden, die man erhält, wenn man auf dem in antero-posteriorer Richtung aufgenommenen Bild vom Kreuzungspunkt des rechten Vorderhofbogens und des Gefässbogens und ebenso von dem höchsten Punkt des Aortenbogens eine Senkrechte auf die Mittellinie zieht (GROEDEL).

Nach v. TEUBERN beträgt die Höhe der normalen Aorta auf dem orthodiographischen Bild gemessen 8.7 cm.

Ich habe das Mass v. TEUBERN's dem Fokus-Filmabstand 150 cm entsprechend, d. h. auf 9.2 cm umgewandelt und dieses als die grösste Höhe der normalen Aorta betrachtet.

### 5. Die Grösse des Herzens.

Bei der Bestimmung der Grösse des Herzens kann man sich mehrerer Methoden bedienen. Ich bespreche von diesen nur eine, den Herz-Lungen-Quotienten. Mit dem Herz-Lungen-Quotienten ist das Verhältnis des transversalen Durchmessers des Herzens zu dem transversalen Durchmesser der Lungen gemeint. Unter dem transversalen Durchmesser der Lungen ist die basale Breite der Lungen zu verstehen. Der transversale Durchmesser des Herzens hinwieder ist gleich dem rechten Medianabstand plus dem linken Medianabstand des Herzens. Als rechter und linker Medianabstand wird die grösste Entfernung des rechten und linken Randes der Herzschaten von der Mittellinie des Körpers bezeichnet (GROEDEL).

Ich habe als normalen Herz-Lungen-Quotienten nach GROEDEL 1:1.90—1:1.99 genommen, obwohl diese Zahlen nicht genau zu meinem Material passen, in dem die Bilder teleröntgenologische (nicht wie bei GROEDEL orthodiagraphische) sind.

## II. Die Grundlagen für die Diagnose Aortitis luetica.

### A. Die heute üblichen.

Die Diagnose der Aortenklappeninsuffizienz und des Aortenaneurysmas lässt sich ziemlich leicht auf Grund der klassischen Symptome stellen. Bei der Diagnose der unkomplizierten Aortitis hat ALLBUTT schon 1915 die grosse Bedeutung der qualitativen Veränderungen des zweiten Aortentones hervorgehoben. Dasselbe haben später mehrere andere Forscher getan. Die Frühdiagnose der Aortitis kann bei Nichtrheumatikern, Nichthypertonikern und Nichtarteriosklerotikern sogar ausschliesslich auf Grund des akzentuierten, metallisch klingenden zweiten Aortentones gestellt werden (ROMBERG 1918, STADLER 1932, PAULLIN 1937). Andere Autoren fordern ausserdem für die Diagnose Aortitis ein

sysolisches Aortengeräusch (JAGIĆ und ZIMMERMANN-MEINZINGEN 1937).

Nach einigen Forschern ist eine sichere Aortitisdiagnose nur durch röntgenologische Feststellung einer Aortenerweiterung möglich (MAYNARD, CURRAN, ROSEN, WILLIAMSON und LINGG 1935, THOMPSON, COMEAU und WHITE 1939).

Auch gibt es Autoren, die sich bei der Diagnose der Aortitis nicht mit einem oder zwei Symptomen begnügen, sondern deren drei bis fünf fordern. So wünschen CARTER und BAKER (1931) für das Diagnostizieren der unkomplizierten syphilitischen Aortitis, dass fünf von den folgenden sieben Kriterien erfüllt sind:

1. Anamnestisch ein verhältnismässig plötzlicher und unerwarteter Anfall der Symptome einer Zirkulationsstörung.

2. Positive Wassermannreaktion.

3. Zunahme der retromanubrialen Dämpfung im zweiten Interkostalraum und Veränderung des zweiten Aortentones. Fluoroskopische Feststellung der Aortendilatation.

4. Fehlen eines Mitralfehlers, eine rheumatische Infektion einbegreifend.

5. Paroxysmale Dyspnoe, meistens nächtliche.

6. Schmerz, vor allem paroxysmaler.

7. Progressive Herzinsuffizienz.

MOORE und andere geben (1932 und 1933) folgende sieben Kriterien an:

1. Teleröntgenographische oder fluoroskopische Feststellung einer Aortendilatation.

2. Vermehrte retromanubriale Dämpfung.

3. Eine Zirkulationsstörung in der Anamnese.

4. Metallische Akzentuierung des zweiten Aortentones.

5. Progressive Herzinsuffizienz.

6. Substernale Schmerzen.

7. Paroxysmale Dyspnoe.

Nach denselben Forschern kann bei einem Patienten mit Spätluës die Diagnose syphilitische Aortitis gestellt werden (mag die Wassermannreaktion im Blute positiv oder negativ sein), wenn bei ihm drei der vorstehenden Kriterien zu konstatieren

sind. Hat der Patient zwei von ihnen, so ist die Diagnose luetische Aortitis wahrscheinlich, vorausgesetzt, dass er keinen Mitraldefekt hat. Falls der Patient negative WR im Blute und in der Anamnese keine Lues hat und falls er auch keine anderen physikalischen Symptome von Lues aufweist, werden für eine sichere Aortitis luetica-Diagnose vier der angeführten Kriterien gefordert.

### *B. Die von mir angewandten.*

Gestützt auf die im Schrifttum geäußerten Ansichten und die Erfahrungen, die ich während meiner Arbeit gemacht habe, begnüge ich mich bei der Stellung der Diagnose unkomplizierte Aortitis, abgesehen von den positiven Luesreaktionen des Blutes, mit dem Nachweis auch nur eines anderen Symptoms bei Nicht-rheumatikern, Nichthypertonikern und Nichtarteriosklerotikern. Eine solche monosymptomatische kardiovaskuläre Lues lag nur in 6 Fällen vor. In 3 Fällen bestand eine Dilatation der Aorta und in 3 Fällen im Ekg eine deutliche Senkung der Strecke ST. Bei den letzteren habe ich keine andere Ätiologie als Lues feststellen können. Mithin dürfte es sich um eine durch die Aortitis hervorgerufene Koronarstenose gehandelt haben. In 42 Fällen war die kardiovaskuläre Lues polysymptomatisch. Von diesen 13 Fälle zeigten 2 Symptome, und zwar 7 eine Aortenerweiterung und im Ekg eine Senkung von ST, 3 eine Dilatation der Aorta und entweder ein systolisches Aortengeräusch oder akzentuierten zweiten Aortenton, 2 ein systolisches Aortengeräusch und akzentuierten zweiten Aortenton bei Nichthypertonikern, Nichtarteriosklerotikern und Nichtrheumatikern und ein Fall stenokardische Schmerzen und im Ekg eine Senkung von ST. In den übrigen Aortitisfällen waren mehrere Symptome festzustellen.

Im folgenden führe ich ausser den positiven Luesreaktionen des Blutes im einzelnen die Symptome an, auf welche hin ich in den verschiedenen Fällen die Diagnose unkomplizierte Aortitiden gestellt habe:

Symptome der unkomplizierten Aortitiden		Zahl der Fälle	
1 Symptom	Aorta dilatiert .....	3	} 6
	Im Ekg Senkung von ST .....	3	
2 Symptome	Aorta dilat. + im Ekg Senkung von ST	7	} 13
	Aorta dilat. + A <sub>2</sub> <sup>1</sup> akzentuiert .....	2	
	Aorta dilat. + syst. Aortengeräusch ....	1	
	A <sub>2</sub> akzentuiert + syst. Aortengeräusch ..	2	
	Stenokard. Schmerzen + im Ekg Senkung von ST .....	1	
3 Symptome	Aorta dilat. + A <sub>2</sub> akzentuiert + syst. Aortengeräusch .....	5	} 16
	Aorta dilat. + stenokard. Schmerzen + im Ekg Senkung von ST .....	3	
	Aorta dilat. + A <sub>2</sub> akzentuiert + im Ekg Senkung von ST .....	3	
	A <sub>2</sub> akzentuiert + syst. Aortengeräusch + im Ekg Senkung von ST .....	4	
	A <sub>2</sub> akzentuiert + syst. Aortengeräusch + stenokard. Schmerzen .....	1	
4 Symptome	Aorta dilat. + A <sub>2</sub> akzentuiert + syst. Aortengeräusch + stenokard. Schmerzen	4	} 12
	Aorta dilat. + A <sub>2</sub> akzentuiert + syst. Aortengeräusch + im Ekg Senkung von ST	3	
	Aorta dilat. + A <sub>2</sub> akzentuiert + stenokard. Schmerzen + im Ekg Senkung von ST	3	
	A <sub>2</sub> akzentuiert + syst. Aortengeräusch + stenokard. Schmerzen + im Ekg Senkung von ST .....	2	
5 Symptome	Aorta dilat. + A <sub>2</sub> akzentuiert + syst. Aortengeräusch + stenokard. Schmerzen + im Ekg Senkung von ST .....	1	1
Zusammen		48	

### III. Die Stichhaltigkeit der Diagnosen.

Von den 91 kardiovaskulären Syphilisfällen meines Materials sind während der Ausführung meiner Arbeit, soviel bekannt, 16 (18 %) gestorben. Von diesen hatten zwei eine unkomplizierte Aortitis. Die übrigen litten vor ihrem Tode an Aortenklappen-

<sup>1</sup> Zweiter Aortenton.



Tabelle  
Zusammenfassung der

Nummer des Falles in der Kasuistik	Klinische Diagnose	Obduktions- diagnose	Geschlecht	Alter	Lues in der Anamnese	Herzbeschwerden und ihre Dauer vor der Diagnose	Exitus nach der Diagnose	RR
64	Aortitis luica.	Aortitis luica.	♂	32	—	½ J. stenokardische Schmerzen.	2 T.	110/80
125	Aortitis luica. Lues cerebro- spin.	Aortitis luica. Hy- peraemia et oe- dema piaie matris.	♀	54	—	½ J. stenokardische Schmerzen. Atem- not.	2 T.	180/80
73	Aortitis luica. In- suff. valv. semilun. aortae. Lues cerebri.	Aortitis luica. Insuff. valv. semilun. aortae. Granula- tiones ependymi ventr. cerebri.	♂	62	—	10 J. Atemnot. ½ J. stenokard. Schmerzen.	2 J.	140/80
65	Aortitis luica. In- suff. valv. semilun. aortae.	Aortitis luica. In- suff. valv. semilun. aortae.	♂	36	—	12 J. Herzklopfen. ½ J. stenokard. Schmerzen.	9 T.	160/80
76	Aortitis luica. In- suff. valv. semilun. aortae.	Aortitis luica. Insuff. valv. semilun. aor- tae.	♂	40	—	1 J. Atemnot und ste- nokard. Schmer- zen.	5 T.	140/40
25	Aortitis luica. Aneurysma aortae. Lues cerebri.	Aortitis luica. Aneu- rysm aortae. Leptomeningitis chr.	♂	45	+	2-3 J. Atemnot und stenokard. Schmerzen.	15 T.	135/70
94	Aortitis luica. Aneurysma aortae.	Aortitis luica. Aneu- rysm aortae.	♂	47	—	2½ Mon. Atemno- t.	1¾ Mon.	155/70
95	Aortitis luica. Aneurysma aortae.	Aortitis luica. Aneu- rysm aortae. Per- foratio in mediast. post. et cavit. pleurae sin.	♂	57	—	2-3 J. Atemnot und stenokard. Schmerzen.	2 J.	140/80
103	Aortitis luica. Aneurysma aortae. Pneu- monia l. dx.	Aortitis luica. Aneu- rysm aortae. Pneumonia l. dx.	♂	38	—	Keine.	7 T.	140/110
82	Aortitis luica. Aneurysma aortae. Insuff. valv. semilun. aortae. Lues cerebri.	Aortitis luica. Aneu- rysm aortae. Lep- tomeningitis chr. Granulationes ependymi ventr. IV cerebri.	♂	34	—	4 Mon. Husten. 1 Mon. Atemnot und stenok. Schmer- zen.	2½ Mon.	210/35

A <sub>2</sub> akzentuiert	Syst. Geräusch	Diast. Geräusch	Pulsus celer	ST im Ekg erniedrigt	Aorta dilatiert		Herz vergrößert		Blut										Zerebrospinalflüssigkeit
					Röntgenolog. Bei der Obduktion	Röntgenolog. Bei der Obduktion	WR I	WR II	KR	MBR II	SR	Hb %	E Mill.	I	Leuk.				
+	+	-	-	+	-	-	-	-	+	+	+	+	43	101	4.990	1.01	9400	Normal	
+	+	-	-	Nicht untersucht	-	-	+	+	+	+	+	+	82	74				Pandy+, Zellen 7.5/mm <sup>3</sup> , WR-	
+	+	+	+	+	+	+	-	+	+	+	+	+	110	83	3.990	1.04	5200	Pandy+, Nonne+, Zellen 31.0/mm <sup>3</sup> , WR+	
-	+	+	+	Nicht untersucht	+	+	+	+	+	+	+	+	8	92	4.870	0.94	8600	Normal	
-	+	+	+	Nicht untersucht	+	+	+	+	+	+	+	+	25	69	3.70	0.98	7800	Nicht untersucht	
+	+	-	-	+	+	+	+	+	+	+	+	+	100	70	3.76	0.93	8000	Pandy+, Nonne+, Zellen 65.0/mm <sup>3</sup> , WR+	
-	-	-	-	+	+	+	-	+	+	+	+	+	105	72	3.83	0.93	14170	Normal	
-	+	-	-	+	+	+	+	+	+	+	+	+	47	84	4.00	1.05	6700	Normal	
-	+	-	-	Nicht untersucht	+	+	Nicht untersucht	+	±	±	+	+	43	84	5.00	0.84	15200	Nicht untersucht	
+	+	+	+	+	+	+	+	+	+	+	+	+	15	81	4.370	0.93	7500	Pandy+, Zellen 25.0/mm <sup>3</sup> , WR+	

insuffizienz oder Aortenaneurysma. Das Alter der Gestorbenen war: 31, 32, 34, 36, 37, 38, 40, 41, 43, 45, 47, 49, 51, 54, 57 und 60 Jahre. Der Altersdurchschnitt betrug für sie 44 Jahre.

Die Obduktion konnte bei 10 ausgeführt werden, nämlich bei den beiden unkomplizierten Aortitisfällen, den 3 Fällen von Aortenklappeninsuffizienz sowie den 5 Fällen von Aortenaneurysma, von denen einer ausserdem Aortenklappeninsuffizienz hatte. *Die klinischen kardiovaskulären Diagnosen stimmten in fast allen Hinsichten mit den Obduktionsdiagnosen überein.* In einem Fall, in dem ich bei dem Lues- plus Hypertoniepatienten die Diagnosen Aortenaneurysma und Aortenklappeninsuffizienz gestellt hatte, konnte jedoch bei der Obduktion nur ein luetisches Aneurysma nachgewiesen werden, während die Aortenklappen völlig normal waren. Es hatte sich wahrscheinlich um eine funktionelle Aortenklappeninsuffizienz gehandelt. GARVIN (1940) hat 14 Fälle gesammelt, in denen bei Hypertoniepatienten Aortenklappeninsuffizienz diagnostiziert wurde, wohingegen die Aortenklappen sich bei der Obduktion als normal erwiesen.

In Tabelle 11 gebe ich eine Zusammenfassung der obduzierten Fälle.

Zu erwähnen ist, dass die Aorta in den beiden unkomplizierten Aortitisfällen nicht erweitert war. Dieser Umstand ist allerdings im Fachschrifttum hervorgehoben worden, aber in der gewöhnlichen klinischen Praxis wird ihm im allgemeinen keine Beachtung geschenkt.

#### IV. Ergebnisse.

##### *Die Häufigkeit und Art der Aortenfehler.*

Aus Tabelle 12 erhellt die Häufigkeit der verschiedenartigen Aortenfehler meines Materials (180 sichere + 19 wahrscheinlich sichere Spätluesfälle) in ihrer Gesamtheit und getrennt nach Geschlecht und Alter sowie danach, ob als ätiologischer Faktor ausschliesslich Syphilis oder ausserdem noch eine andere Krankheit vorgelegen hat. Die Abbildungen 10—13 zeigen anschaulicher die Frequenz der Aortenfehler bei Männern und Frauen verschiedenen Alters.

Die an Spällues leidenden Individuen haben in 45.7 % Aortenfehler. Von diesen sind unkomplizierte Aortitiden 24.1 %, Aortenklappeninsuffizienzen 14.1 % und Aneurysmen 7.5 %.

Unter den Aortenklappeninsuffizienzen finden sich 5 Fälle, die nicht ohne weiteres als sicher luetisch bezeichnet werden können, weil 4 von ihnen auch in der Anamnese eine rheumatische Infektion haben und einer auch an Endocarditis lenta leidet. Von den mit rheumatischer Infektion Behafteten sind jedoch 3 ziemlich alt (49, 51 und 62 Jahre), weshalb ich geneigt bin, ihre Aortenklappeninsuffizienz am ehesten als luetisch aufzufassen.

Aortenaneurysmen sind bei den Männern wahrscheinlich zahlreicher als bei den Frauen anzutreffen ( $12.4 \pm 3.2 \% - 2.1 \pm 1.5 \% = 10.3 \pm 3.5 \%$ ).<sup>1</sup> Andere Aortenfehler kommen dagegen bei den Männern und Frauen ungefähr in gleicher Menge vor. Der luetische Aortenprozess macht somit bei den Frauen meist bei der Aortitis halt, während er sich bei den Männern bis zum Aneurysma weiterentwickelt.

<sup>1</sup> Die mittleren Fehler  $\{\varepsilon(p)\}$  aller in dieser Arbeit direkt gefundenen Prozentzahlen (p) sind berechnet aus der Formel

$$\varepsilon(p) = \pm \sqrt{\frac{p(100-p)}{n}}$$

wo n die Gesamtzahl der Fälle ist. Der mittlere Fehler  $\varepsilon(p_1 - p_2)$  der Differenz  $p_1 - p_2$  zweier Prozentzahlen, z. B. von  $p_1$  und  $p_2$ , ist andererseits so gross wie die Quadratwurzel aus der Summe der Quadrate der mittleren Fehler des Subtrahenden und des Minuenden, d. h.

$$\varepsilon(p_1 - p_2) = \sqrt{\varepsilon^2(p_1) + \varepsilon^2(p_2)}.$$

Um zu beurteilen, ob die Differenz zweier gefundener Prozentzahlen wirklich ist oder ob sie sich verändern könnte, falls uns ein anderes Material zur Verfügung stände, habe ich folgende allgemein gebräuchliche statistische Regel angewandt:

1. Wenn das Verhältnis der Differenz der Prozentzahlen zum mittleren Fehler des Unterschieds  $\geq 3$  ist, bedeutet dies ein *sicheres* Ergebnis,
2.  $\rightarrow \leftarrow$   $= 3-2$   $\rightarrow \leftarrow$  ein *wahrscheinliches* Ergebnis,
3.  $\rightarrow \leftarrow$   $= 2-1$   $\rightarrow \leftarrow$  ein *mögliches* Ergebnis,
4.  $\rightarrow \leftarrow$   $= 1-0$   $\rightarrow \leftarrow$  , dass keine eigentliche Differenz vorliegt.

Tabelle  
Die Häufigkeit

Alter Jahre	Ge- schlecht	Zahl der Unter- suchten	Ätio-				
			Syphilis	Syphilis + Hypertonie	Aortitis Zusammen		Syphilis
			Aortitis				Aorten- suffi-
			Anzahl	Anzahl	Anzahl	%	Anzahl
0—19.....	♂	—	—	—	—	—	
20—29.....	♂	14	3	—	3	21.4	—
30—39.....	♂	33	10	—	10	30.3	4
40—49.....	♂	33	6	—	6	18.2	2
50+ .....	♂	25	2	—	2	8.0	2
Zusammen	♂	105	21		21	20.0	8
0—19.....	♀	1	—	—	—	—	—
20—29.....	♀	9	—	—	—	—	—
30—39.....	♀	30	11	—	11	36.7	3
40—49.....	♀	24	7	1	8	33.3	2
50+ .....	♀	30	5	3	8	26.7	1
Zusammen	♀	94	23	4	27	28.7	6
Summe	♂ + ♀	199	44	4	48	24.1	14

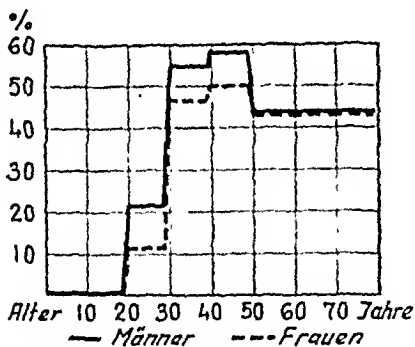
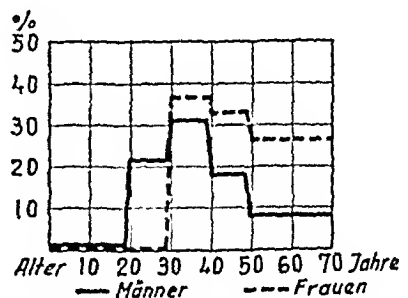
Abbildung 10. Die Aortenfehler  
zusammen.

Abbildung 11. Die Aortitiden.

12.  
der Aortenfehler.

logie

Syphilis + eine andere Krankheit	Aorten- klappen- insuffizienz Zusammen		Syphilis	Syphilis	Syphilis + Hypertonic	Aneurysma und Aneu- rysm + Aorten- klappen- insuffizienz Zusammen		Aortenfehler Zusammen	
klappenin- zienz	Anzahl	%	Aneurys- ma	Aneurysma + Aortenklappen- insuffizienz		Anzahl	%	Anzahl	%
—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	3	21.4
2	6	18.2	1	—	1	2	6.1	18	54.5
3	5	15.2	5	2	1	8	24.2	19	57.9
4	6	24.0	1	1	1	3	12.0	11	44.0
9	17	16.2	7	3	3	13	12.4	51	48.6
—	—	—	—	—	—	—	—	—	—
1	1	11.1	—	—	—	—	—	1	11.1
—	3	10.0	—	—	—	—	—	14	46.4
1	3	12.5	—	1 <sup>1</sup>	—	1	4.1	12	50.0
3	4	13.3	—	—	1	1	3.3	13	43.3
5	11	11.7	—	1	1	2	2.1	40	42.5
14	28	14.1	7	4	4	15	7.5	91	45.7

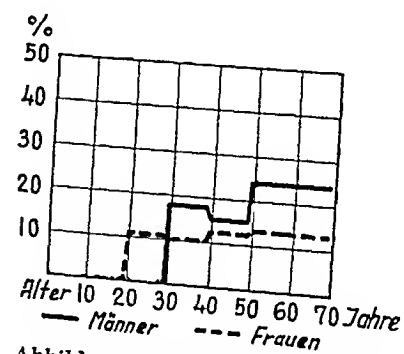


Abbildung 12. Die Aortenklappen-  
insuffizienzen.

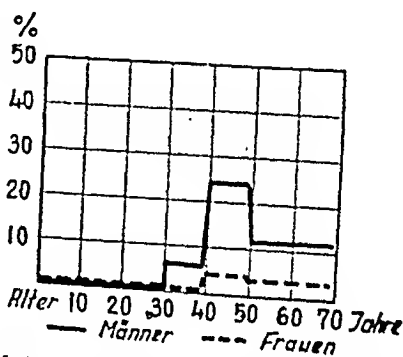


Abbildung 13. Die Aneurysmen und  
Aneurysmen + Aortenklappen-  
insuffizienzen.

<sup>1</sup> Aneurysma aortae abdominalis.

Tabelle 13.

Vergleich über die Häufigkeit der kardiovaskulären Lues in einigen Ländern.

Autor	Land	Jahr	Grösse und Art des Materials	Antiluetische Behandlung	Häufigkeit der kardiovaskulären Lues												
BRUUS-GAARD, E.	Norwegen	1928	473 Syphilispatienten	Keine	12.8 %												
STRELOW, K.	Deutschland	1921—25	1,112 Luespatienten eines Krankenh. f. innere Medizin	Keine	12.3 %												
BRUHNS, C.	Deutschland	1926	129 Patienten eines Krankenh. f. Hautkrankheiten	Keine	23.3 % (sichere + wahrscheinliche + suspekta zus. 38.8 %)												
TURNER, T.	U.S.A.	1936	10,000 Syphilispatienten	?	Weisse { Männer 8.7 % Frauen 4.8 % } 7.2 % Neger { Männer 17.9 % Frauen 7.2 % } 11.4 % } 10.1 %												
MAYNARD, Jr. et al.	U.S.A.	1935	346 Syphilispatienten (des Brooklyn Hospital)	?	41.9 %												
COLE und USILTON	U.S.A.	1936	6,253 Syphilispatienten	Keine (der grösste Teil)	<table><tr><td></td><td>Aortitis</td><td>Aortenklappeninsuffizienz</td><td>Aneurysma</td></tr><tr><td>Weisse</td><td>3.7</td><td>3.4</td><td>0.7</td></tr><tr><td>Neger</td><td>10.4</td><td>7.2</td><td>3.1</td></tr></table>		Aortitis	Aortenklappeninsuffizienz	Aneurysma	Weisse	3.7	3.4	0.7	Neger	10.4	7.2	3.1
	Aortitis	Aortenklappeninsuffizienz	Aneurysma														
Weisse	3.7	3.4	0.7														
Neger	10.4	7.2	3.1														
VONDERLEHR, R. et al.	U.S.A.	1936	399 bei einer Massenuntersuchung festgestellte KR-positive Syphilispatienten (Neger)	Keine	7.7 % mit Luesinfektion vor 3 J 12.0 % „ „ „ 6 J 14.9 % „ „ „ 9 J												
KEMP und COCHEMS	U.S.A.	1937	1,000 Syphilispatienten des Public Health Institute	Keine	12.7 %												
MAIJALA, P.	Finnland	1942	199 bei systematischer Untersuchung an einer medizinischen Poliklinik festgestellte WR + oder KR + oder MBR II + Syphilispatienten	Keine (der grösste Teil)	<table><tr><td>Aortitis</td><td>24.1 %</td></tr><tr><td>Aortenklappeninsuffizienz</td><td>14.1 %</td></tr><tr><td>Aneurysma</td><td>7.5 %</td></tr></table> } 45.7 %	Aortitis	24.1 %	Aortenklappeninsuffizienz	14.1 %	Aneurysma	7.5 %						
Aortitis	24.1 %																
Aortenklappeninsuffizienz	14.1 %																
Aneurysma	7.5 %																

Die ausländische Literatur bietet zahlreiche Untersuchungen über die Frequenz der kardiovaskulären Lues. In Tabelle 13 vergleiche ich meine eigenen Ergebnisse mit denen anderer Forscher.

Die kardiovaskuläre Lues entwickelt sich also in jedem von der Tabelle berücksichtigten Land in beachtlicher Menge, wobei die Prozentzahlen jedoch ziemlich stark variieren. In meinem Material findet sie sich mehr als in den Materialien der anderen von mir angeführten Autoren.

Das Alter der an kardiovaskulärer Lues Leidenden verteilt sich in meinem Material ziemlich gleichmässig auf die Jahre zwischen 30 und 60. Patienten unter 30 sowie über 60 Jahren sind nur spärlich anzutreffen. R. SIEVERS hat aus Finnland (1902) 7 luetische Aortitisfälle veröffentlicht, wobei es von Interesse ist, dass einer seiner Fälle über 50 Jahre und die anderen 38—44 Jahre alt waren. Im grossen und ganzen also dieselbe Altersverteilung wie bei meinen kardiovaskulären Luespatienten. Die ausländischen Forscher geben ebenfalls an, dass bei den 40- bis 50jährigen am meisten kardiovaskuläre Lues zu finden ist (u. a. MOORE, DANGLADE und REISINGER 1932, KEMP und COCHEMS 1937, KAMPMEIER 1938, WILE und SNOW 1938).

### *Die Beziehung zwischen der antiluetischen Therapie und der Entwicklung der kardiovaskulären Lues.*

Durch Tabelle 14 soll veranschaulicht werden, wie die antiluetische Therapie auf die Entwicklung der kardiovaskulären Lueeingewirkt hat. Nur ein geringer Teil meiner Fälle hat überhaupt antiluetische Behandlung erhalten. Sind einem Patienten mit

Tabelle 14.

Die Beziehung der Entwicklung der kardiovaskulären Syphilis zur antiluetischen Behandlung.

Therapie (vor der Feststellung der Krankheit)	Zahl der Fälle	Aortitiden		Aneurysmen und Aortenklappeninsuffizienzen		Zusammen	
		Anzahl	%	Anzahl	%	Anzahl	%
Keine .....	155	37	23.9	34	21.9	71	45.8
Unvollständige ..	38	8	21.1	9	23.7	17	44.8



destens 30 Injektionen Neosalvarsan + Schwermetall-, Wismut- oder Quecksilbersalz gegeben worden, so nehme ich an, dass er eine vollständige Kur bekommen hat. Eine weniger umfassende Behandlung betrachte ich als unvollständig.

Wir bemerken, dass sich die kardiovaskuläre Lues bei den unbehandelten Patienten in gleichem Umfang wie bei denen mit unvollständiger Therapie entwickelt hat. Über die mit vollständiger antiluetischer Therapie behandelten Patienten lässt sich in dieser Beziehung wegen der Knappheit meines Materials nichts aussagen. Es gibt Forscher, nach deren Ansicht sogar eine unbedeutende antiluetische Therapie einigermaßen hemmend auf die Entstehung luetischer Aortenfehler einwirken würde. So soll die Tendenz dieser Wirkung günstig sein (HELLER 1922), während nach der Meinung anderer Forscher eine ungenügende antiluetische Behandlung sich umgekehrt in der Weise äussert, dass sie die Zeit zwischen der Primärinfektion und dem Auftreten der kardiovaskulären Symptome verkürzt (WILMANN 1925, JUNGMAHN und HALL 1926). Mein Material gibt keine weiteren Aufschlüsse über die zuletzt erwähnte Frage.

### *Die Neurolues im Zusammenhang mit luetischen Aortenfehlern.*

Die Häufigkeit der im Zusammenhang mit luetischen Aortenfehlern vorkommenden Neurolues ergibt sich aus Tabelle 15.

Aus Tabelle 15 wird ersichtlich, dass 60 % aller mit einem

**Tabelle 15.**  
Die Neurolues im Zusammenhang mit luetischen Aortenfehlern.

Diagnose	Zahl der Fälle	Neurolues	
		Anzahl	%
Aortitis .....	48	33	69
Aortenklappeninsuffizienz .....	25	15	60
Aneurysma und Aneurysma + Aortenklappeninsuffizienz .....	13	4	30
Zusammen	86	52	60

Aortenfehler behafteten Patienten auch an Neurolues leiden. In dem weiter unten folgenden Kapitel über Neurolues wird sich herausstellen, dass Neurolues in meinem ganzen Material im gleichen Masse (d. h. in 61.2 %) anzutreffen ist. So findet sich bei Aortenlues also Neurolues nicht mehr und nicht weniger als bei anderer Lues.

1930—1936 konstatierten WILE und SNOW bei 210 Patienten mit kardiovaskulärer Lues eine Abnormität der Pupillen in 23 %, und die 73 Aortenaneurysmapatienten COLE's und USILTON's hatten in 31 % Neurolues. Die ausländischen Forscher haben also bei Patienten mit Aortenlues weniger Neurolues festgestellt als ich. Hierauf werde ich später zurückkommen.

### *Die Hypertonie bei Spätlues.*

Tabelle 16 und Abbildung 14 veranschaulichen die Hypertonie bei meinen Spätluespatienten. Als Hypertonie habe ich in Übereinstimmung mit mehreren Forschern einen Blutdruck über 140/90 mm Hg betrachtet (u. a. ALLEN und MUSSER, FAUGHT, ROBINSON und BRUCER).

*Meine Spätluespatienten hatten also systolische Hypertonie in 27.1 % und diastolische in 21.1 %. Bei den Männern und Frauen tritt Hypertonie im gleichen Masse auf.*

Bei uns hat KERPPOLA (1930) nachgewiesen, dass Tabetiker eine Neigung zu erhöhtem Blutdruck haben. BRIN und GEROUX haben eine Zusammenfassung gemacht und konstatiert, dass der prozentuale Anteil der Syphilis an der Hypertonie in der Literatur zwischen 18 und 90 % schwankt. Doch begegnet man Forschern, nach denen die Lues überhaupt nicht oder nur in mässigem Grade Hypertonie im Gefolge hat (CHIAPPINI 1926, WOLFF 1926).

Abbildung 15 zeigt den durchschnittlichen systolischen Blutdruck meiner Spätluesfälle im Vergleich zu dem durchschnittlichen systolischen Blutdruck, den ROBINSON und BRUCER (1939) bei 7,478 nichtsyphilitischen Männern fanden. Der durchschnittliche Blutdruck ist mithin bei meinen Syphilitikern höher als bei den Nichtsyphilitikern.

*Es scheint, dass die Spätlues in meinem Material auf die eine oder andere Weise eine Erhöhung des Blutdruckes verursacht hat.*

**Tabelle 16.**  
Der Blutdruck bei Spätlues

Alter Jahre	Ge- schlecht	Zahl der Fälle	Syst. Blutdruck über 140 mm Hg		Diast. Blutdruck über 90 mm Hg	
			Anzahl	%	Anzahl	%
unter 29 ..	♂	14	1	7.1	1	7.1
30—39.....	♂	33	3	9.1	5	15.1
40—49.....	♂	33	11	33.3	9	27.3
50—59.....	♂	17	8	47.1	1	5.9
60 und mehr	♂	8	5	62.5	3	37.5
Zusammen	♂	105	28	26.7	19	18.1
unter 29 ..	♀	10	1	10.0	1	10.0
30—39.....	♀	30	2	6.7	3	10.0
40—49.....	♀	24	6	25.0	4	16.7
50—59.....	♀	17	6	35.3	6	35.6
60 und mehr	♀	13	11	84.6	9	69.2
Zusammen	♀	94	26	27.7	23	24.5
Summe	♂ + ♀	199	54	27.1	42	21.1

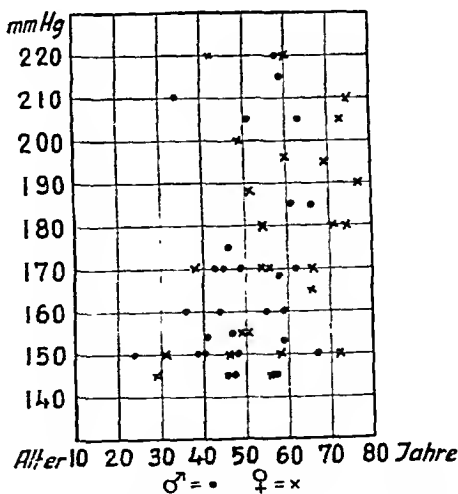


Abbildung 14. Der systolische Blutdruck in den Hypertoniefällen.

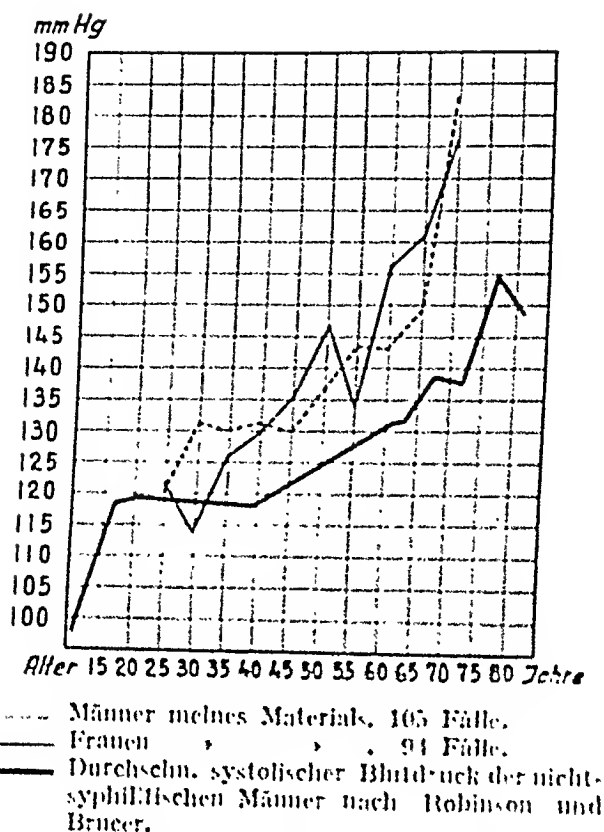


Abbildung 15. Der Mittelwert des systolischen Blutdruckes bei Spätluccs.

## Das klinische Bild der Aortenfehler.

### A. Das subjektive Bild.

Die in der Anamnese der Aortenluesfälle auftretenden Beschwerden, die auf Affektionen der Kreislauforgane hinweisen, werden aus Tabelle 17 ersichtlich.

Aus der Tabelle geht hervor, dass jeder zweite Patient mit unkomplizierter Aortitis keine auf eine Erkrankung der Kreislauforgane hinweisenden Beschwerden gehabt hat. Die Aortitis ist somit asymptomatisch verlaufen.

Nicht wenige Forscher haben ihre Aufmerksamkeit dem Begriff der asymptomatischen Aortitis zugewandt, hauptsächlich aber erst in letzter Zeit (LANGER 1926, MAYNARD, Jr., CUNNAN,

**Tabelle 17.**  
Die subjektiven Beschwerden bei Aortenlues.

Beschwerden	Aortitis (48 Fälle)		Aortenklappenin- suffizienz (28 Fälle)		Aneurysma (15 Fälle)	
	Zahl der Fälle	Fälle in %	Zahl der Fälle	Fälle in %	Zahl der Fälle	Fälle in %
Keine Beschwerden .....	25	52	1	4	1	7
Stenokard. Schmerzen ....	16	33	16	57	9	60
Atemnot .....	3	6	24	86	12	80
Herzklopfen .....	6	13	7	25	4	27
Husten .....	—	—	2	7	4	27
Schwindel .....	1	2	1	4	1	7
Brennende Schmerzen ....	1	2	—	—	—	—
Heiserkeit .....	—	—	—	—	2	13

ROSEN, WILLIAMSON und LINGG 1935, PAULLIN 1937, WILSON, Jr. 1937, WILE und SNOW 1938). Auch meine Untersuchungen zeigen, wie wichtig es ist, über das Vorhandensein einer asymptomatischen Aortitis Bescheid zu wissen.

Wenn eine unkomplizierte Aortitis *Beschwerden* hervorgerufen hat, sind diese hauptsächlich als stenokardische Schmerzen aufgetreten. Solche Schmerzen haben 33 % der Patienten gehabt, und sie sind vorzugsweise präkordial gewesen. JAGIĆ und ZIMMERMANN—MEINZINGEN geben stenokardische (präkordiale) Schmerzen bei ihren Aortitispatienten in 50 %, HOCHREIN in 40 % und MOORE, DANGLADE und REISINGER in 17.9 % an.

Im Gegensatz zu den unkomplizierten haben die komplizierten luetischen Aortenprozesse in bedeutendem Grade Beschwerden ausgelöst. Bei den Patienten mit Aortenklappeninsuffizienz und Aortenaneurysma liessen sie fast die gleiche Beschaffenheit und Frequenz erkennen. Von diesen Beschwerden steht an erster Stelle Dyspnoe, die überwiegend durch kardiale Dekompensation verursacht war; sie war in 80—86 % anzutreffen. Die zweite Stelle nahmen die stenokardischen Schmerzen ein, die in 57—60 % vorkamen. Von KAMPMEIER (1938) wurden bei Fällen von Aortenaneurysma Schmerzen in 60 % und von GLENDY, CASTLEMAN und WHITE (1937) ebenso bei dem grössten Teil ihrer Patienten konstatiert.

Die Dauer der in der Anamnese auftretenden Beschwerden erhellt aus Tabelle 18.

Tabelle 18.

Die Dauer der Beschwerden (in Jahren) vor der Diagnose.

Beschwerden in der Anamnese	Aortitis Dauer der Beschwerden in Jahren			Aortenklappen- insuffizienz Dauer der Beschwerden in Jahren			Aneurysma und Aneu- rysm + Aorten- klappeninsuffizienz Dauer der Beschwerden in Jahren		
	Kür- zeste	Läng- ste	Durch- schnitt- liche	Kür- zeste	Läng- ste	Durch- schnitt- liche	Kür- zeste	Läng- ste	Durch- schnitt- liche
Schmerzen .....	2/12	10	2	6/12	6	3	1/12	3	2
Atemnot .....	6/12	10	6	3/12	14	4	1/12	4	2
Herzklopfen .....	6/12	10	4	6/12	14	6	6/12	4	2
Husten .....	—	—	—	6/12	3	16/12	3/12	26/12	1
Schwindel .....	3/12	3/12	3/12	3	3	3	3/12	3/12	3/12
Brennende Schmer- zen .....	—	—	—	—	—	—	—	—	—
Heiserkeit .....	—	—	—	—	—	—	1/12	4/12	2/12

Sowohl in den unkomplizierten als den komplizierten Fällen bestanden vor der Feststellung der Krankheit durchschnittlich 2—4 Jahre Beschwerden von der Krankheit, aber die Anamnese kann auch sehr kurze Zeit, nur 1—3 Monate, umfassen. Manche Aortenfälle können in bezug auf den Krankheitsverlauf vom Beginn der subjektiven Beschwerden an sehr bösartig sein. Dabei kann der Verlauf dem eines Karzinoms gleichgestellt werden. So finden sich in meinem Material ein Aneurysmafall und 2 Fälle mit Aortenklappeninsuffizienz (Fall 91, 82 und 101 in der Kasuistik), die innerhalb 4 Monate nach dem Auftreten der subjektiven Beschwerden starben.

Tabelle 19 zeigt, dass in den Fällen von komplizierter Aortenlues durchschnittlich 16—36 Jahre von der Primärinfektion bis zum Beginn der subjektiven Beschwerden und etwas längere Zeit bis zur Feststellung der Krankheit vergangen sind. Die ausländischen Forscher geben als Dauer dieses Intervalls im Durchschnitt 15—23,4 Jahre an (ROMBERG 1918, MAYNARD, Jr., CURRAN, ROSEN, WILLIAMSON und LINGG 1935).

Tabelle 19.

Intervall von der Luesinfektion bis zum Beginn der subjektiven Beschwerden und der Feststellung der Krankheit.

Diagnose	Therapie	Intervall von der Primärinfektion (in Jahren)			
		bis zum Beginn der subjektiven Beschwerden		bis zur Feststellung der Krankheit	
		In den verschiedenen Fällen	Durchschn.	In den verschiedenen Fällen	Durchschn.
Aortitis	Unvollst.	—	—	7; 9; 13; 13; 14; 15; 15; 17; 18; 18; 19; 41.	16
Aortenklappeninsuffizienz	Unvollst.	6; 7; 15; 16 6/12; 24; 31.	16	8; 10; 17; 18; 28; 36.	19
Aortenklappeninsuffizienz	Keine	34; 38.	36	38; 40.	39
Aneurysma	Unvollst.	19; 21; 21; 27; 33.	24	21; 22; 26; 28; 36.	26

### B. Das objektive Bild.

Aus Tabelle 20 ergeben sich die objektiven Befunde, die im Status der Aortenluesfälle meines Materials anzutreffen sind. In Tabelle 21 vergleiche ich die Befunde, die ich bei den unkomplizierten Aortitiden konstatiert habe, mit den Befunden ausländischer Forscher.

In meinen Fällen von Aortenlues findet man ein systolisches Aortengeräusch in 68 %, akzentuierten II. Aortenton in 51 % und eine röntgenologisch nachweisbare Erweiterung der Aorta in 74 %. Bei den unkomplizierten Aortitiden und bei Aortenklappeninsuffizienz kommt eine Aortendilatation ungefähr in gleicher Menge vor (73 bzw. 61 %). Eine Herzerweiterung zeigt sich am häufigsten bei Aortenklappeninsuffizienz, wo ungefähr die Hälfte der Fälle eine solche aufweist. Ein Inkompensationszustand des Herzens tritt am meisten bei Aortenklappeninsuffizienz auf (79 %). Meine Ergebnisse decken sich annähernd mit denen der ausländischen Forscher.

Abbildung 16 veranschaulicht im Röntgenbild die Länge des transversalen Durchmessers des Aortenbogens in meinen Fällen von Aortenlues, Abbildung 17 die Länge der Aorta ascendens und Abbildung 18 die Beträge des Kreuzfuchs-Masses.

Tabelle 20.

Die objektiven Befunde bei den syphilitischen Aortenfehlern.

Diagnose	Zahl der Fälle	Systol. Aorten- geräusch		Diastol. Geräusch		II. Aortenton akzentuiert und metallisch		Aorta röntgenolo- gisch erweitert		Herz röntgenolo- gisch erweitert		Herz inkom- pensiert	
		Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%
Aortitis.....	48	24	50	—	—	30	63	35	73	2	4	2	4
Aortenklappeninsuf- fizienz .....	28	27	96	28	100	10	36	17	61	16	57	22	79
Aneurysma und An- eurysma + Aorten- klappeninsuffizienz	15	11	73	8	53	6	40	15	100	5	33	5	33
Zusammen	91	62	68	36	40	46	51	67	74	23	25	29	32



Tabelle 21.

Die Veränderungen bei den unkomplizierten Aortitiden. Vergleich der Ergebnisse verschiedener Autoren.

Autor	Land	Jahr	Systol. Aort- tengeräusch %	II. Aorten- ton akzentuiert %	Aorta rönt- genologisch erweitert %	Herz rönt- genologisch erweitert %	Herz inkon- spensiert %
ROMBERG, E. ....	Deutschland	1918			Fast immer		
HOCHREIN, M. ....	Deutschland	1931	70	80	100		
STADLER, E. ....	Deutschland	1932	50				
MOORE, DANGLADE und REISIN- GER .....	U.S.A.	1932		25.8	86		
MAYNARD, JR. et al. ....	U.S.A.	1935				32.2	
KEMP und COCHEMS .....	U.S.A.	1937			59		
WILSON, JR., R. ....	U.S.A.	1937					32.1
WILE und SNOW .....	U.S.A.	1938	51	72			
MAIJALA, P. ....	Finnland	1942	50	63	73	4	4

Im grössten Teil meiner Fälle beträgt die Länge des transversalen Durchmessers des Aortenbogens 7.5—9 cm, die der Aorta ascendens 4.0—6 cm und Kreuzfuchs 3—4 cm. Mithin sind die Masse des transversalen Durchmessers des Aortenbogens und der Aorta ascendens durchschnittlich 0.5—2 cm und das Kreuzfuchs-Mass 1 cm grösser als normal. Die grössten der Masse sind bei den 40- bis 50jährigen anzutreffen.

Die *elektrokardiographischen* Veränderungen werden aus Tabelle 22 ersichtlich. Mit SCHERF (1937) betrachte ich als normale PQ-Strecke 0.12—0.20 Sek. und als normale QRS-Strecke 0.05—0.10 Sek. Q<sub>III</sub> fasse ich als normal auf, wenn es unter 25 % von der Höhe der grössten R-Zacke beträgt. Verläuft ST über 0.10 mm unterhalb der isoelektrischen Linie, so betrachte ich es als erniedrigt.

Die ST-Strecke weist in bemerkenswertem Grade Veränderungen auf: sie ist bei den unkomplizierten Aortitiden in 73 %, bei Aortenklappeninsuffizienz in 63—89 % und bei Aneurysmen in 100 % erniedrigt. Dagegen lässt die T-Zacke nur selten Veränderungen erkennen. Ein Lävogramm ist häufig zu finden. In Fällen, in deren Ätiologie neben Syphilis eine andere Krankheit, Arteriosklerose, Hypertonie oder Infectio rheumatica vorliegt, kommt

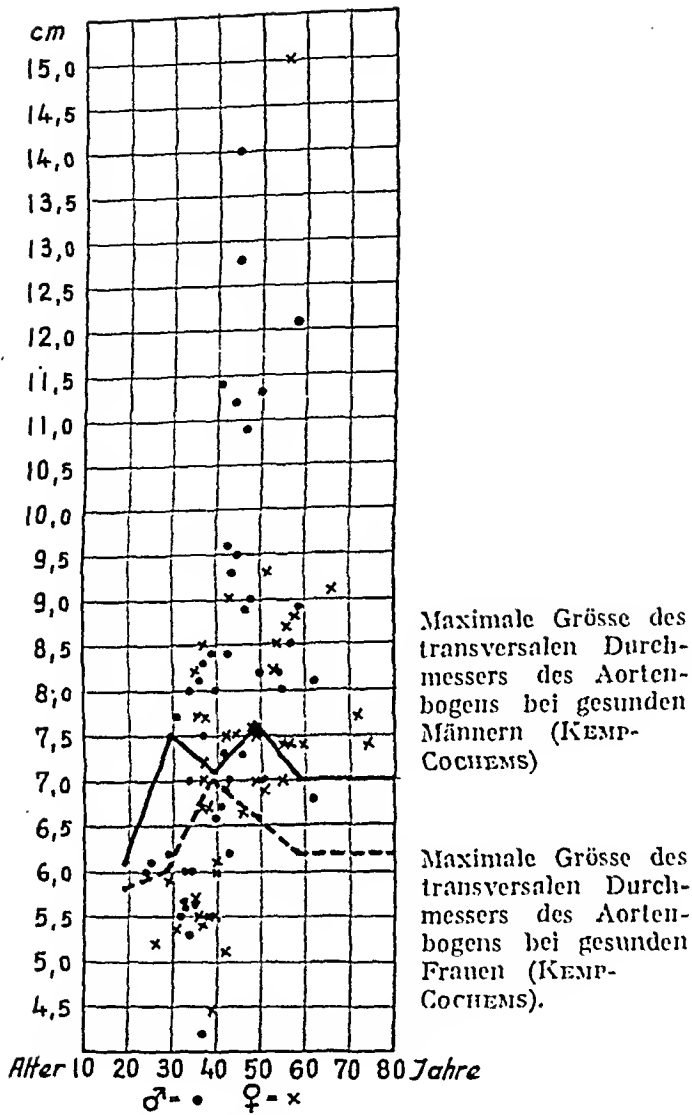


Abbildung 16. Die Grösse des transversalen Durchmessers des Aortenbogens in den Fällen von Aortenlues.

öfter ein Lävogramm vor als in den ausschliesslich durch Syphilis verursachten Fällen. Andersartige Ekg-Veränderungen sind nur in unbedeutendem Masse vertreten. So war PQ nur in 3 Fällen verlängert, Q<sub>III</sub> war in einem Fall zu tief, und Vorhofflimmern wurde desgleichen in einem Fall beobachtet. Im allgemeinen bestanden in meinen Fällen von Aortenlues mehr Ekg-Veränderungen als in denen mancher anderen Forscher (JUSTER und PARDEE, MAYNARD, Jr., CURRAN, ROSEN, WILLIAMSON und LINGG).

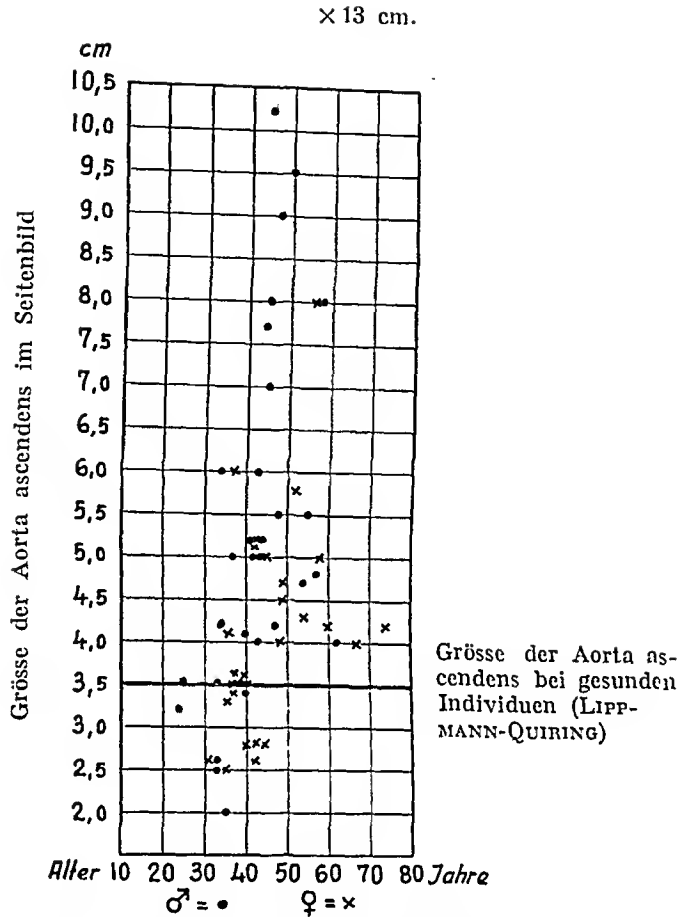


Abbildung 17. Die Größe der Aorta ascendens in den Fällen von Aortenlues.

Aus Tabelle 23 ersehen wir die Ergebnisse der *Luesreaktionen* im Blute. Die Tabelle zeigt nicht, in welchem Grade die verschiedenen Luesreaktionen positiv oder suspekt sind, da ich die seronegative kardiovaskuläre Lues nicht in mein Material aufgenommen habe. Doch ist aus der Zusammenstellung zu entnehmen, dass WR I in meinen Fällen von kardiovaskulärer Lues in 46—73 % positiv, in 13—18 % suspekt und in 13—36 % negativ ist, je nach der Art der kardiovaskulären Lues. Mithin kann WR I auch in schwereren Fällen von Aortenlues negativ sein. Bei WR II, KR und MBR II kommen ebenfalls negative Resultate vor, wiewohl in geringerem Masse als bei WR I.

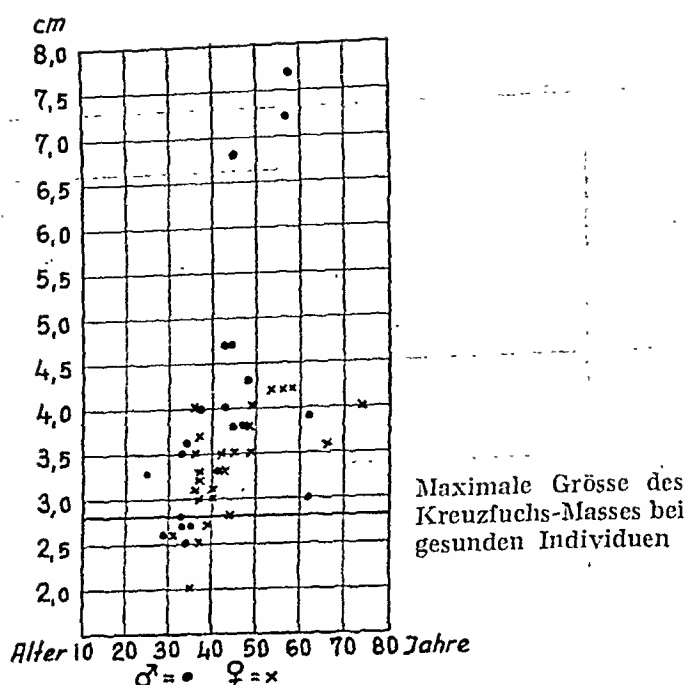


Abbildung 18. Die Grösse des Kreuzfuchs-Masses in den Fällen von Aortenlues.

Diese Ergebnisse sprechen für die Auffassung der Serologen, dass die Ausführung mehrerer serologischer Reaktionen notwendig ist.

### Zusammenfassung.

Bei den Spätluespatienten findet man in Finnland Aortenfehler in 45.7 %. Von diesen haben unkomplizierte Aortitiden 24.1 %, Aortenklappeninsuffizienzen 14.1 % und Aneurysmen 7.5 %. Aortenaneurysmen sind wahrscheinlich bei den Männern mehr als bei den Frauen anzutreffen. Andere Aortenfehler kommen dagegen bei den Männern und den Frauen ziemlich gleich häufig vor.

In Finnland entwickelt sich bei den Luespatienten, die keine oder unvollständige antiluetische Behandlung erhalten haben, Aortenlues mit grösserer Frequenz als in Norwegen, Deutschland und USA.

Das Alter der an Aortenlues Leidenden hat ziemlich gleichmässig zwischen 30 und 60 Jahren gelegen.

Unvollständig durchgeführte antiluetische Therapie scheint auf die Entwicklung der kardiovaskulären Lues weder hemmend noch fördernd einzuwirken.

Tabelle  
Die Ekg-

Die Ekg-

Ätiologie	Diagnose	Zahl der Fälle	ST erniedrigt								
			0.2— 0.5 mm		0.6— 1.0 mm		≥ 1.1 mm		Zusam- men		
			Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	
Syphilis	Aortitis	40	In irgendeiner Ab- leitung	12	30	13	33	4	10	29	73
Syphilis + Hyper- tonie	Aortitis	3	In irgendeiner Ab- leitung	—	—	1	33	1	33	2	66
Syphilis	Aortenklappeninsuf- fizienz	11	In irgendeiner Ab- leitung	2	18	2	18	3	27	7	63
Syphilis + eine an- dere Krankheit (Hy- pertonia, Infect. rheum., Endocardi- tis lenta)	Aortenklappeninsuf- fizienz	9	In irgendeiner Ab- leitung	1	11	—	—	7	78	8	89
Syphilis	Aortenaneurysma und Aortenaneu- rysm + Aorten- klappeninsuffizienz	7	In irgendeiner Ab- leitung	2	29	2	29	3	42	7	100
Syphilis + Hyper- tonie	Aortenaneurysma und Aortenaneu- rysm + Aorten- klappeninsuffizienz	4	In irgendeiner Ab- leitung	—	—	2	50	2	50	4	100

Im Zusammenhang mit Aortenfehlern kommt Neurolyues in 60 % vor.

Bei den Spätluespatienten findet man systolische Hypertonie in 27.1 % und diastolische in 21.1 %.

Von den an unkomplizierter Aortitis leidenden Patienten hatte jeder zweite keine auf eine Erkrankung der Kreislauforgane hinweisende subjektive Beschwerde. Wenn eine unkomplizierte Aortitis Beschwerden verursacht hat, traten sie hauptsächlich unter der Form von stenokardischen Schmerzen auf. Die komplizierten Aortenfehler

## 22.

## Veränderungen.

T-Zacke isoelekt. oder negativ				PQ verlängert		QIII- Zacke zu tief		Fibrillatio auric.		In der R-Zacke Knoten.						Lävo- gramm	
T <sub>1</sub>		T <sub>2</sub>								RI		RII		RIII			
Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%
1	3	1	3	1	3	1	3	—	—	7	18	10	25	19	48	4	10
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	9	—	—	—	—	1	9	—	—	1	9	—	—	2	18
3	33	2	22	—	—	—	—	—	—	5	56	4	44	5	56	5	56
1	14	—	—	1	14	—	—	—	—	—	—	—	—	—	—	4	57
—	—	—	—	1	25	—	—	—	—	—	—	—	—	—	—	3	75

dagegen lösten in grosser Menge Beschwerden, besonders unter der Form von Dyspnoe und stenokardischem Schmerz aus. Sowohl in den Fällen von unkomplizierten als von komplizierten Aortenprozessen betrug die Dauer der subjektiven Beschwerden vor der Feststellung der Krankheit durchschnittlich 2—4 Jahre, doch konnte sie auch sehr kurze Zeit, nur 1—2 Monate, umfassen.

Mein Material enthält einen Fall mit Aneurysma und 2 Fälle mit Aortenklappeninsuffizienz, die innerhalb 4 Monate nach dem Beginn der subjektiven Beschwerden an ihrer Krankheit starben.

Tabelle 23.

Die Ergebnisse der serologischen Luesreaktionen des Blutes bei kardiovaskulärer Lues.

		Zahl der untersuchten serologischen Reaktionen	Ergebnisse					
			Posit. (+)		Susp. ( $\pm$ und $-\frac{1}{2}$ )		Negat.	
			Anzahl	%	Anzahl	%	Anzahl	%
Aortitis (48 Fälle)	WR I	48	28	58	6	13	14	29
	WR II	48	36	75	3	6	9	19
	KR	48	44	92	—	—	4	8
	MBR II	40	36	90	2	5	2	5
Aortenklappeninsuffizienz (28 Fälle)	WR I	28	13	46	5	18	10	36
	WR II	28	14	50	8	29	6	21
	KR	28	26	93	—	—	2	7
	MBR II	24	20	83	—	—	4	17
Aneurysma und Aneurysma + Aortenklappeninsuffizienz (15 Fälle)	WR I	15	11	73	2	13	2	13
	WR II	15	12	80	3	20	—	—
	KR	15	14	93	—	—	1	7
	MBR II	13	12	92	—	—	1	8

NB. Endocarditis lenta bei 1 Pat., Infectio rheum. bei 2 Pat.

*Mithin ist der Verlauf der Krankheit ein sehr maligner gewesen.*

*Von der Primärinfektion bis zum Auftreten der kardiovaskulären Symptome sind 16—36 Jahre verstrichen.*

*In den Fällen von Aortenlues war die Aorta auf dem in 1 ½ m Fokus-Filmabstand aufgenommenen Röntgenbild durchschnittlich um 0.5—2 cm erweitert und das Kreuzfuhs-Mass um 1 cm verlängert. Im Ekg waren in erheblichem Masse Veränderungen festzustellen. So war die ST-Strecke bei den Aortitiden in 73 %, bei den Aortenklappeninsuffizienzen in 63—89 % und bei den Aneurysmen in 100 % erniedrigt.*

*Schliesslich sei erwähnt, dass die klinischen Diagnosen in den 10 Fällen, in denen eine Obduktion ausgeführt wurde, fast in jeder Beziehung mit den Obduktionsdiagnosen übereinstimmten.*

## Die neurologischen Veränderungen.

### I. Methodik.

Ausser der Anamnese und einer klinischen Untersuchung habe ich bei 193 der betreffenden 199 Spätluespatienten eine Untersuchung des Liquors ausgeführt. Dieser wurde durch Lumbalpunktion entnommen. Damit die Patienten nach der Punktion keine Kopfschmerzen bekommen sollten, entnahm ich sehr wenig Liquor und liess die Patienten danach in der Poliklinik zuerst zwei Stunden auf dem Bauch und darauf noch eine Stunde auf dem Rücken liegen. Hiernach durften sie in ihre Wohnung gehen mit der Aufforderung, bis zum folgenden Tage im Bett zu bleiben. Heftigere Kopfschmerzen haben nach der Punktion nur 4 Patienten gehabt.

An der Lumballflüssigkeit wurden folgende Untersuchungen ausgeführt:

1. Eiweissbestimmungen.
2. Eine Zählung der Zellen.
3. Serologische Luesreaktionen und Kolloidreaktionen.
4. Zuckerbestimmungen.

1. Eiweissbestimmungen. Die Eiweissuntersuchungen der Lumballflüssigkeit machte ich sofort nach der Punktion mit Hilfe der Pandy- und der Nonne-Reaktion. Diese sind schon ursprünglich so eingestellt, dass sie im normalen Liquor ein negatives Resultat geben. Jedoch ist festgestellt worden, dass die Pandy-Reaktion auch unter physiologischen Verhältnissen mitunter eine eben wahrnehmbare Opaleszenz gibt. Aus diesem Grunde habe ich eine eben wahrnehmbare Opaleszenz als negativ betrachtet. Eine deutliche Opaleszenz habe ich mit Pandy  $\pm$  bezeichnet, Trübung oder Niederschlag mit Pandy+ bzw. ++.

2. Zählung der Zellen. LEVISON (1919) betrachtet als normale Zellzahl des Liquors 4—6 je  $\text{mm}^3$  und als pathologische erst über 10 Zellen je  $\text{cm}^3$ . Nach späteren Forschern ist die Zellzahl des normalen Liquors kleiner. So enthalten  $\text{cm}^3$  Liquor nach NEEL's (1928) der normale Liquor 1—2 Zellen und DEMME hält (1935) die Zellzahl für normal, wenn sie unter 10 liegt.



Ich habe als normale Zellzahl in Übereinstimmung mit DEMME bis  $8/3$  ( $= 2.7$ ) Zellen je  $\text{mm}^3$  angenommen. Bei meinen Untersuchungen wurde die Zählung der Zellen sofort nach der Punktion mit einer Türkschen Zählkammer ausgeführt.

3. Serologische Luesreaktionen und Kolloidreaktionen. Die Wassermann-Reaktion ist im Liquor in bezug auf die Lues weitgehend spezifisch. Unspezifische positive Wassermann-Reaktionen kommen nur bei Lepra, Frambösie und Trypanosomiasis sowie möglicherweise bei tuberkulöser und citriger Meningitis vor. Die Müllersche Ballungsreaktion ist im Liquor gleichfalls weitgehend spezifisch. Die in der Praxis üblichen Kolloidreaktionen sind so eingestellt, dass der normale Liquor in beliebiger Verdünnung entweder keine oder nur geringfügige Veränderungen zeigt (DEMME 1935).

Bei meinen Untersuchungen wurde sowohl die gewöhnliche als die mit cholesterinisiertem Extrakt sensibilisierte Wassermann-Reaktion geprüft. Die Technik war dieselbe wie bei der Untersuchung des Serums, nur waren die Liquormengen nicht die gleichen wie hier. Die Zerebrospinalflüssigkeit wurde unverdünnt in einer Menge von 1.0 und 0.5  $\text{cm}^3$  (Gesamtmenge 2.5  $\text{cm}^3$ ) angewandt. Da der Liquor kein Blut enthielt, wurde er gewöhnlich aktiviert benutzt. Genügte die Menge der Lumbalflüssigkeit, so wurde die Müllersche »Ballungsreaktion II« nach Müllers Originalmethode geprüft, desgleichen die Mastix- und Goldsolreaktion. Die Ergebnisse der Mastixreaktion habe ich nach Art der Resultate der Goldsolreaktion durch Ziffern bezeichnet, und zwar durch 0—5, wobei 0, 1 und 2 bedeuten, dass die Flüssigkeit im Röhrchen klar (unverändert), schwach trübe bzw. milchig war, 3, dass ein kleiner und 4, dass ein grosser Niederschlag vorlag, und 5, dass eine vollständige Ausflockung stattgefunden hatte. Bei der Beurteilung der Mastixreaktion habe ich erst das Vorhandensein eines kleinen Niederschlags (3,000,000,000) als pathologisch angesehen. Diese Untersuchungen sind von Dozent OLOF SIEVERS am Serobakteriologischen Institut der Universität Helsinki ausgeführt worden.

4. Zuckerbestimmungen. Der Zuckergehalt des normalen Liquors schwankt zwischen 45 und 75 mg % (DEMME 1935). Bei meinen Untersuchungen wurde die Zuckerbestimmung in 22 Fällen an der Lumbalflüssigkeit nach der Methode von Hagedorn aus-

geführt. Da alle betreffenden Zuckerwerte innerhalb normaler Grenzen lagen, ist es mir nicht angezeigt erschienen, noch mehr Bestimmungen zu machen.

## II. Ergebnisse.

### *Häufigkeit und Art der Neurolues.*

Tabelle 24 zeigt die Häufigkeit der Veränderungen im Zentralnervensystem bei den Spätluespatienten. Die Fälle habe ich nach dem Alter und Geschlecht sowie ausserdem danach gruppiert, ob die Zerebrospinalflüssigkeit Veränderungen aufwies oder nicht. Die Veränderungen andererseits habe ich in schwere und leichte eingeteilt.

*Schwere* Liquorveränderungen lagen nach meiner Auffassung dann vor, wenn der Liquor ausser anderen Veränderungen positiven Ausfall einer oder beider Wassermann-Reaktionen oder der Müllerschen »Ballungsreaktion II« zeigte. Dieser Gruppe habe ich ferner die Fälle hinzugefügt, in denen WR I im Liquor  $\pm$  war (2 Fälle).

Um *leichte* Liquorveränderungen schien es sich mir dann zu handeln, wenn beide Wassermann-Reaktionen und die Müllersche »Ballungsreaktion II« negativ waren, aber der Liquor andere Veränderungen zeigte: Vermehrung des Eiweisses oder der Zellen oder deutliche Veränderungen in der Mastixreaktion. Diese Gruppe habe ich je nachdem, ob mit den Liquorveränderungen Pupillen- und Reflexstörungen kombiniert waren oder nicht, in zwei Untergruppen eingeteilt. Zu der ersten von diesen gehören 29 Fälle. Neben den Pupillen- und Reflexstörungen war in allen diesen Fällen das Eiweiss des Liquors vermehrt und in 17 Fällen auch die Zellen, oft sogar beträchtlich. Alle derartigen Fälle habe ich als solche von sicherer Neurolues aufgefasst. Das Adiesche Syndrom kann ja auch nicht in Betracht kommen, da in sämtlichen Fällen Liquorveränderungen bestanden (BERGMARK). Zu der zweiten Untergruppe gehören 17 Fälle, in denen allen sowohl das Eiweiss des Liquors als die Zellmenge erhöht waren, aber Pupillen- und Reflexstörungen fehlten. Die Liquorveränderungen dieser Fälle können nicht ohne weiteres auf Lues zurückgeführt werden,

**Tabelle 24.**  
Die Häufigkeit der Neuroloes.

Alter in Jahren	Geschlecht	Zahl der Untersuchten	Neuroloues mit schweren Liquorveränderungen				Neuroloues mit leichten Liquorveränderungen				Neuroloues ohne Liquorveränderungen		Neuroloues zusammen	
			WR I oder WR II oder MBR II posit. (+)	WR I susp. (±)	Zusammen		Pupillen- und Reflexstörungen	Ohne Pupillen- und Reflexstörungen	Zusammen					
			Anzahl	Anzahl	Anzahl	%	Anzahl	Anzahl	Anzahl	%	Anzahl	%	Anzahl	%
0—19 .....	♂	—	—	—	—	—	—	—	—	—	—	—	—	—
20—29 .....	♂	14	5	—	5		1	2	3		—		8	57.1
30—39 .....	♂	33	15	—	15		1	2	3		2		20	60.7
40—49 .....	♂	31	10	1	11		3	3	6		1		18	58.1
50+ .....	♂	24	4	—	4		8	1	9		1		14	58.3
Zusammen	♂	102	34	1	35	34.3	13	8	21	20.6	4	3.9	60	58.8
0—19 .....	♀	1	—	—	—		—	—	—		—		—	—
20—29 .....	♀	9	4	—	4		1	1	2		—		6	66.6
30—39 .....	♀	28	10	1	11		7	3	10		—		21	75.0
40—49 .....	♀	23	7	—	7		4	—	4		1		13	56.5
50+ .....	♀	30	8	—	8		4	5	9		2		18	60.0
Zusammen	♀	91	29	1	30	32.9	16	9	25	27.5	3	3.3	58	63.7
Summe ♂ + ♀		193	63	2	65	33.7	29	17	46	23.9	7	3.6	118	61.2

möglicherweise sind sie durch eine andere Krankheit hervorgerufen worden. Indessen habe ich auch die letzterwähnte Gruppe zu den durch Lues verursachten Veränderungen im Zentralnervensystem gerechnet, da ich in den meisten Fällen keine andere Ätiologie habe finden können.

Die Neuroloes *ohne Liquorveränderungen* bildet die dritte Gruppe. Es handelte sich um Fälle mit Schwindel und Kopfschmerz, in denen diese Symptome nach Verabreichung spezifischer Therapie aufhörten. Solcher Fälle waren 5 zu zählen. Ausserdem habe ich mit dieser Gruppe einen Fall von Opticusatrophie und auch einen anderen Fall vereinigt. Dieser letztere, eine 71jährige Frau, bei der die Luesreaktionen im Blut positiv waren, hatte nur Pupillenstö-

rungen und geschwächte Patellarreflexe. Hier könnte es sich um das ADIESCHE Syndrom handeln.

*Bei den an Spätlues leidenden Patienten kommen Veränderungen im Zentralnervensystem zusammen in 61.2 % vor.*

Neurolues mit ausgeprägten Liquorveränderungen findet man in 33.7 %, mit leichten Liquorveränderungen in 23.9 % und ohne Liquorveränderungen in 3.6 %. Bei den Männern und Frauen treten Veränderungen im Zentralnervensystem mathematisch betrachtet in gleicher Menge auf. NELSON und CRAIN (1938) erwähnen, dass klinisch feststellbare Neuroveränderungen bei lueskranken Frauen deutlich weniger als bei Männern vorkommen. Meine Befunde hinwieder zeigen, dass, wenn man seine Untersuchungen weiter führt, bei beiden Geschlechtern Neuroveränderungen in gleichen Masse anzutreffen sind. Die Frauen haben also nur auffälligere Neuroveränderungen weniger. In bezug auf das

Tabelle 25.

Die Häufigkeit der Neurolues in einigen Ländern.

Auton	Land	Jahr	Grösse und Art des Materials	Neurolues in %
GULDBERG, G. ....	Norwegen	1896—1930	481 bei der Obduktion festgestellte Syphilisfälle	13.53
NICKEL, H. ....	Deutschland	1907—1933	827 bei der Obduktion festgestellte Syphilisfälle	30.07
RONBERG, E. ....	Deutschland	1918	695 an einer internen Klinik festgestellte Syphilisfälle	33.7
STRELOW, K. ....	Deutschland	1921—1925	1.112 Syphilisfälle einer internen Klinik	34.2
MELCHIOR, L. ....	Dänemark	1914—1920	358 bei der Obduktion festgestellte Syphilisfälle	21.0
MOORE, J. ....	U.S.A.	1935	399 bei einer Massenuntersuchung festgestellte KR-positive Syphilisfälle, die keine antiluetische Behandlung bekommen hatten (Neger)	25.0
VON DEN LEHR, R. .	U.S.A.	1936		26.1
PARRAN, T. ....	U.S.A.	1937		30.0
HJELMANN, J. ....	Finnland	1892	1860 klinisch festgestellte Syphilisfälle	14.0
MAIJALA, P. ....	Finnland	1942	193 bei systematischer Untersuchung an einer medizinischen Poliklinik festgestellte WR-, KR- und MBR H-positive Syphilisfälle	61.2

*Alter* standen die, an Neurolues leidenden Patienten zwischen 20 und 60 Jahren. In keiner Altersgruppe ist Neurolues in grösserer Menge als in den anderen zu konstatieren.

Aus Finnland liegt von früherer Zeit her eine Arbeit über die Häufigkeit der Neurolues vor. Sie stammt von HJELMMAN (1892), dessen 1860 Fälle tertiärer Syphilis umfassendes Material zu 14 % Gehirnsyphilis enthielt. Indessen lässt sich sein Ergebnis nicht genau mit dem meinigen vergleichen, weil bei den Patienten seines Materials die Zerebrospinalflüssigkeit nicht untersucht worden ist.

Im ausländischen Schrifttum begegnet man mehreren Angaben über die Häufigkeit der Lues des Zentralnervensystems. In Tabelle 25 stelle ich die Untersuchungsergebnisse aus einigen Ländern zusammen.

*Wie man sieht, entwickelt sich in Finnland bei den nicht und den unvollständig mit antiluetischer Therapie behandelten Luespatienten in bedeutendem Grade mehr Neurolues als in Norwegen, Deutschland, Dänemark und den Vereinigten Staaten.*

„The Committee on Nonspecific Therapy of Neurosyphilis“<sup>1)</sup> hat bezüglich der Art der Neurolues eine moderne Klassifikation aufgestellt. Bei der Gruppierung meiner eigenen Fälle nach der Beschaffenheit habe ich in den Hauptzügen diese Klassifikation befolgt, dabei aber meine Einteilung etwas vereinfacht. Meine Gruppierung sieht folgendermassen aus:

1. Asymptomatische Neurolues.
2. Meningeale Neurolues = mindestens 100 Zellen/mm<sup>3</sup> (SOLOMON).
3. Vaskuläre (reine) Neurolues.
4. Tabo-paralytische Neurolues.
5. Tabes dorsalis (klassische).
6. Tabes dorsalis-ähnliche Encephalomyelitis (leichte Tabes dors.).
7. Parkinsonismus-ähnliche Neurolues.

Aus Tabelle 26 ergibt sich die Häufigkeit der verschiedenen Neuroluesarten in meinem Material. Die meisten Patienten sind leichte Fälle von Encephalomyelitis mit Pupillenstörungen und

<sup>1)</sup> J. amer. med. Assoc. 109, 1163 (1937).

geschwächten oder erloschenen Patellarreflexen. Klassische Tabes und Paralyse sind äusserst spärlich zu finden. Asymptomatische, meningeale und reine vaskuläre Neurolues kommen ziemlich gleich viel vor.

Meine Erfahrungen über die Häufigkeit der leichten Tabes dorsalis decken sich mit den Untersuchungsergebnissen des Deutschen ROMBERG von 1918. Auch in seinem Material war die Tabes gutartig, und dabei waren nur Pupillen- und Reflexstörungen zu konstatieren. Andere Neuroluesformen treten in meinem Material gleichfalls im grossen und ganzen in demselben Verhältnis auf wie in dem der anderen Forscher (MOORE und FAUPEL 1928, COLE und USILTON 1936).

*Die Beziehung zwischen der antiluetischen Therapie und der Entwicklung der Neurolues.*

Die Beziehung der antiluetischen Therapie zur Häufigkeit der Neurolues sowie der verschiedenen Formen zueinander wird aus Tabelle 27 und Abbildung 19 ersichtlich. Die unvollständig Behandelten haben gewöhnlich nur etwa 10 Neosalvarsan- oder Wismutinjektionen bekommen.

Tabelle 26.  
Die Formen der Neurolues.

Form der Neurolues	Im Liquor WR + oder MIBR II + (65 Fälle)		Im Liquor WR — und MIBR II — (53 Fälle)		Zusammen (118 Fälle)	
	An- zahl	%	An- zahl	%	An- zahl	%
Asymptomatisch .....	8	12.3	10	18.9	18	15.2
Meningeal .....	15	23.1	—	—	15	12.7
Vaskulär (rein) .....	4	6.2	12	22.6	16	13.6
Tabo-paralytisch .....	1	1.5	—	—	1	0.9
Tabes dorsalis (klassische) .....	3	4.6	—	—	3	2.5
Tabes dorsalis-ähnliche leichte Encephalomyelitis ..	34	52.3	30	56.6	64	54.2
Parkinsonismus .....	—	—	1	1.9	1	0.9
(das Zittern hörte durch Malaria- und antiluetische Therapie auf)						

Tabelle 27.

Die Beziehung der Entwicklung der Neurolues zu der antiluetischen Behandlung.

Behandlung	Zahl der Fälle	Neurolues mit schweren Liquorveränderungen		Neurolues mit leichten Liquorveränderungen und ohne Liquorveränderungen		Zusammen	
		Anzahl	%	Anzahl	%	Anzahl	%
Keine .....	150	54	36.0	34	22.6	88	58.6
Unvollständige	37	10	27.0	16	43.2	26	70.2

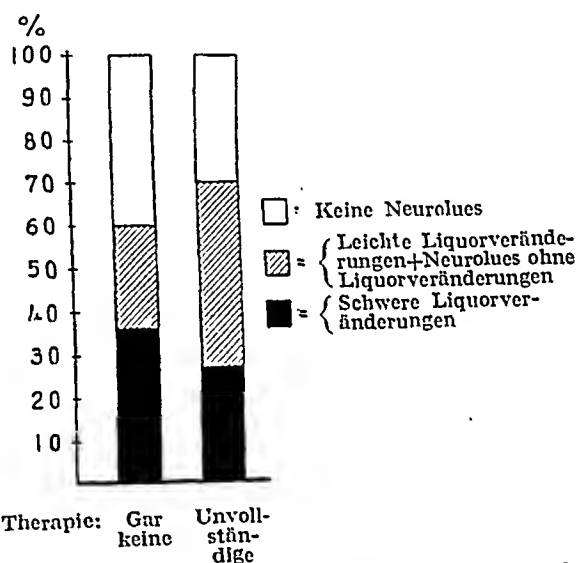


Abbildung 19. Das Verhältnis der antiluetischen Therapie und der Häufigkeit und verschiedenen Formen der Neurolues zueinander.

Bei den nicht antiluetisch Behandelten entwickelt sich Neurolues mit schweren Liquorveränderungen möglicherweise mehr als bei denen, die unvollständige antiluetische Therapie erhalten haben:

$$36.0 \pm 3.9 \% - 27.0 \pm 7.3 \% = 9.0 \pm 8.2 \%$$

Bei den unvollständig antiluetisch Behandelten entsteht dagegen wahrscheinlich mehr Neurolues mit leichten Liquorveränderungen.

rungen und ohne Liquorveränderungen als bei den nicht antiluetisch Behandelten:

$$43.2 \pm 8.2 \% - 22.6 \pm 3.4 \% = 20.6 \pm 8.9 \%$$

Bei denen, die unvollständige antiluetische Therapie erhalten haben, entwickeln sich alle Neuroluesformen zusammen möglicherweise mehr als bei den nicht antiluetisch Behandelten:

$$70.2 \pm 7.5 \% - 58.6 \pm 4.0 \% = 11.6 \pm 8.5 \%$$

### *Die luetischen Aortenfehler im Zusammenhang mit Neurolues.*

Die Häufigkeit der in den Neuroluesfällen meines Materials vorkommenden luetischen Aortenfehler wird aus Tabelle 28 deutlich.

GÜRICH hat auf Grund der Sektionen, die 1913—1924 in Deutschland ausgeführt worden sind, nachgewiesen, dass sich die bei Zerebrospinalues auftretende luetische Aortitis bei den Männern auf 48 % und bei den Frauen auf 69.5 % beläuft. Ebenso hat COENEN (1926) gleichfalls in Deutschland konstatiert, dass 42.9 % von 147 obduzierten Paralytikern einen luetischen Aortenfehler hatten. Die Ergebnisse der auf dieselbe Frage bezüglichen Untersuchungen der Deutschen LÖWENBERG (1924) und FRISCH (1932) werden aus den Tabellen 29 und 30 ersichtlich.

**Tabelle 28.**  
Die Häufigkeit luetischer Aortenfehler bei Neurolues.

	Zahl der Fälle	Aortitis		Aortenklappeninsuffizienz		Aneurysma und Aneurysma + Aortenklappeninsuffizienz		Zusammen	
		Anzahl	%	Anzahl	%	Anzahl	%	Anzahl	%
Neurolues mit schweren Liquorveränderungen .....	65	18	27.7	7	10.8	2	3.1	27	41.6
Neurolues mit leichten und ohne Liquorveränderungen	53	15	28.3	8	15.1	2	3.8	25	47.2
Zusammen	118	33	27.9	15	12.7	4	3.4	52	44.0



Tabelle 29.  
(Nach K. LÖWENBERG).

Art der Nervenerkrankung	Gesamt- zahl	Ohne Aortitis	Mit Aortitis	%
Paralyse .....	341	228	113	33,1
Lues cerebri .....	9	6	3	33

Tabelle 30.  
(Nach F. FRISCH).

Art der Nerven- erkrankung	Gesamtzahl	Ohne Aortitis	Mit Aortitis	Prozent Verhältnis
Progr. Paralyse ..	38	27	11	29 %
Tabes dorsalis ....	54	28	26	48 %
Lues cerebrospinalis	23	15	8	34,8 %
Gesamtzahl .....	115	70	45	39

Die Aorta war also in meinem Material bei Neurolues in 44 % und in dem Material der deutschen Forscher zwischen 29 und 69.5 % syphilitisch affiziert.

## Das klinische Bild der Neurolues.

### A. Das subjektive Bild.

Die Art und Häufigkeit der subjektiven Beschwerden, die auf eine Affektion des Zentralnervensystems hinweisen, ist in Abbildung 20 wiedergegeben. *Mehr als ein Drittel der Patienten hatten keine auf einen Krankheitszustand im Zentralnervensystem deutende Beschwerde.* Trotz der negativen Anamnese über das Nervensystem kann der klinische oder Liquorbefund sehr wohl positiv sein. Die häufigste der subjektiven Beschwerden war *Kopfschmerz*. Mitunter waren die Beschwerden der Patienten recht allgemeiner Natur, wie *Müdigkeit* und *Abmagerung*. Nachdem die Patienten antiluetische Behandlung erhalten haben, hat die Müdigkeit aufgehört und haben die Patienten angefangen zuzunehmen. Bemerkenswert ist, dass 10 Patienten *Bauchbeschwerden* hatten, die

durch antiluetische Therapie verschwanden. Sie waren auf keine Weise von der Art wie die akuten, heftigen Schmerzen, die gastrischen Krisen, die bei der klassischen *Tabes dorsalis* vorkommen, sondern erinnerten mehr an unbestimmte, lange andauernde dyspeptische Beschwerden. Während meiner Tätigkeit als stellvertretender Assistenzarzt am Krankenhaus Lapinlahti gab ich 8 dieser Patienten Malariafieber + spezifische Behandlung. 2 Patienten bekamen nur spezifische Behandlung. Später haben sämtliche 10 Patienten mitgeteilt, dass sie sich wohl befinden und von

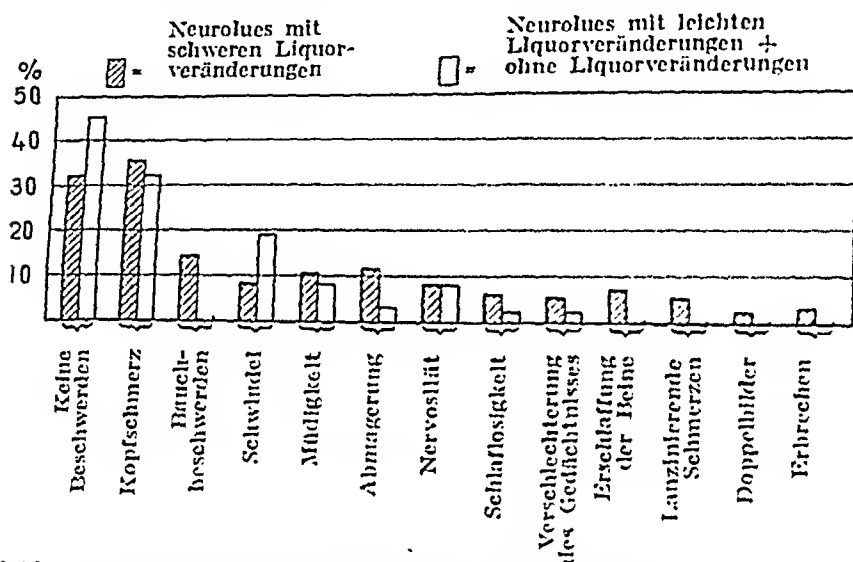


Abbildung 20. Die auf Erkrankungen des Nervensystems der Neurosyphilispatienten hinweisenden subjektiven Beschwerden.

ihren Beschwerden befreit sind. Zwei Patienten hatten *Erbrechen*, der eine während fünf Jahre und der andere während eines Jahres. Nachdem sie Malariafieber und antiluetische Therapie erhalten hatten, liess das Erbrechen nach.

In der Neurosyphilisgruppe, in der der Liquor starke Veränderungen zeigte, waren die anamnestischen Beschwerden heftiger als in derjenigen, welche im Liquor leichte oder gar keine Veränderungen aufwies.

In den wenigen Fällen, in denen der Beginn der Luesinfektion bekannt ist, hat die Zeit zwischen dieser und dem Auftreten der subjektiven Beschwerden der Neurosyphilis durchschnittlich 16 Jahre betragen. Nach KRABBE (1937) umfasst dieses Intervall bei *Tabes*

dorsalis 10—15 Jahre. In der früher erwähnten Arbeit HJELMAN's aus Finnland vom Jahre 1892 belief es sich durchschnittlich auf rund 6 Jahre. Während der letzten 50 Jahre hat sich also in Finnland die Latenzzeit zwischen der Luesinfektion und dem Auftreten der Nervensymptome offenbar *verlängert*. Die Lues ist bei uns in dieser Hinsicht *benigner* geworden, was wahrscheinlich auf einer sich allmählich entwickelnden Immunität beruht.

### B. Das objektive Bild.

Die Frequenz der bei der objektiven Untersuchung hervortretenden Veränderungen bei Neurolues wird durch die Abbildungen 21 und 22 veranschaulicht.

Wir sehen, dass, obwohl WR und MBR II im Liquor positiv sind, sein Eiweiss und seine Zellzahl doch nicht immer eine Erhöhung zeigen. In diesen Fällen war Pandy positiv in 92 %, Nonne in 62 % und die Zellzahl erhöht in 80 %. Der Liquor enthielt überhaupt keine Zellen in 7.7 % (5 Fälle). Pupillenstörungen

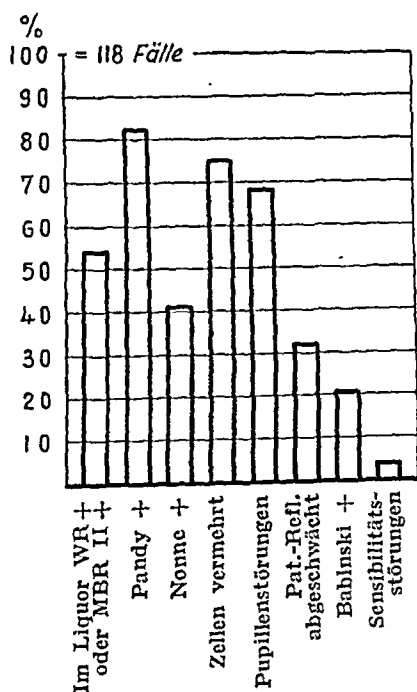


Abbildung 21. Sämtliche Neuroluesfälle. Die Häufigkeit der objektiven pathologischen Veränderungen.

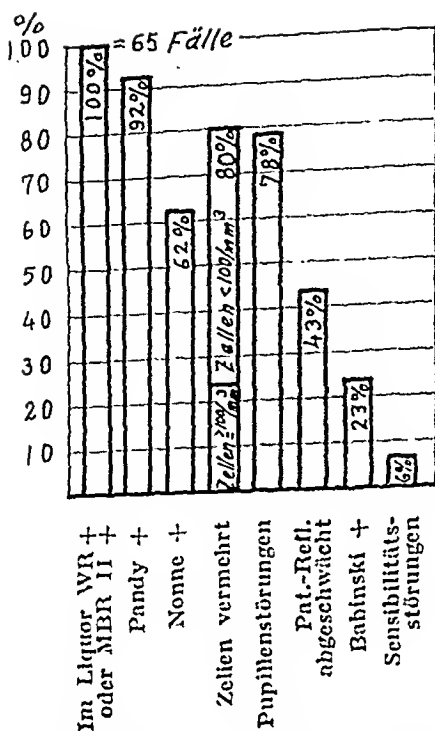


Abbildung 22. Die Neuroluetfälle mit schweren Liquorveränderungen. Die Häufigkeit der objektiven pathologischen Veränderungen.

waren in 78 % anzutreffen, die Patellarreflexe waren geschwächt oder erloschen in 43 %, und Babinski war positiv in 23 %. Sensibilitätsstörungen traten nur in 6 % auf.

Ein Vergleich der Ergebnisse, die die serologischen Luesreaktionen im Blut bei den verschiedenen Neuroluetformen geliefert haben, ist in Tabelle 31 angestellt. Es ist zu beachten, dass mein Material aus Fällen zusammengestellt ist, in denen mindestens eine der geprüften Luesreaktionen im Blut positiv oder suspekt war.

Bei der Neuroluet, die starke Veränderungen im Liquor zeigte, waren WR I (1) und KR (2) im Blut wahrscheinlich und WR II (3) und MBR II (4) möglicherweise in höherem Grade positiv als bei der Neuroluet, die leichte oder gar keine Veränderungen im Liquor aufwies:

1.  $68 \pm 5.9 \% - 49 \pm 6.9 \% = 19 \pm 9.0 \%$ .
2.  $99 \pm 1.2 \% - 89 \pm 4.3 \% = 10 \pm 4.5 \%$ .
3.  $77 \pm 5.2 \% - 62 \pm 6.7 \% = 15 \pm 8.5 \%$ .
4.  $93 \pm 3.4 \% - 86 \pm 5.4 \% = 7 \pm 6.4 \%$ .

Tabelle 31.

Die Ergebnisse der serologischen Luesreaktionen des Blutes bei Neurolues.

	Reaktion	Zahl der ge- prüf- ten Reak- tionen	Ergebnisse					
			Positiv (+)		Suspekt ( $\pm$ , —?)		Negativ (—)	
			An- zahl	%	An- zahl	%	An- zahl	%
Neurolues mit schweren Liquor- veränderungen (65 Fälle) ..	WR I	65	44	68	11	17	10	15
	WR II	65	50	77	10	15	5	8
	KR	65	64	99	1	2	—	—
	MBR II	57	53	93	1	2	3	5
Neurolues mit leichten und ohne Liquorveränderungen (53 Fälle)	WR I	53	26	49	9	17	18	34
	WR II	53	33	62	10	19	10	19
	KR	53	47	89	—	—	6	11
	MBR II	42	36	86	3	7	3	7

Ausserdem ist zu bemerken, dass die serologischen Luesreaktionen des Blutes in Neuroluesfällen, in denen die WR im Liquor positiv war, ziemlich oft, WR I sogar in 15 %, negativ waren.

### Zusammenfassung.

Bei den Spätluespatienten findet man in Finnland Veränderungen im Zentralnervensystem in 61.2 %. Im Liquor konstatiert man positive WR oder MBR II in 33.7 %. In den anderen Fällen von Neurolues sind WR und MBR II des Liquors negativ.

Bei Männern und Frauen tritt Neurolues prozentual in gleicher Menge auf. Zum grössten Teil hat man es mit Fällen von leichter Encephalomyelitis zu tun. Klassischer Tabes und Paralyse begegnet man ausserordentlich selten.

In Finnland entwickelt sich bei unbehandelten und unvollständig behandelten Luespatienten bedeutend mehr Neurolues als in Norwegen, Deutschland, Dänemark und USA.

Bei Luespatienten, die keine antiluetische Therapie bekommen haben, entwickelt sich Neurolues mit ausgeprägten Liquorveränderungen möglicherweise häufiger und Neurolues mit leichten und ohne Liquorveränderungen wahrscheinlich seltener als bei unvollständig antiluetisch behandelten.

In den Neuroluesfällen war die Aorta in 44 % luetisch affiziert.

Das Alter der Neuroluespatienten variierte ziemlich gleichmässig zwischen 20 und 60 Jahren.

Mehr als ein Drittel der Neuroluespatienten hatten von ihrer Krankheit keine subjektiven Beschwerden. Bei den Patienten mit subjektiven Beschwerden war am häufigsten Kopfschmerz festzustellen.

### Blutveränderungen.

#### Das Blutbild.

In meinem Material sind die Hämoglobinwerte (korrigiert) bei 196 Spätluespatienten bestimmt worden. Die roten Blutkörperchen wurden bei 178 und die weissen Blutkörperchen bei 175 Kranken gezählt. Dies geschah sowohl bei den roten als den weissen Blutkörperchen mit der Türkschen Zählkammer. Die Resultate werden aus den Tabellen 32—36 ersichtlich.

Wenn man nach Tabelle 36 als normale (korrigierte) Hämoglobinwerte bei den finnischen Männern mindestens 85 % und bei

Tabelle 32.

Die Hämoglobinwerte (korrigiert) bei Spätlues. Fälle 196 (♂ 104. ♀ 92).

Hgb %	Ge- schlecht	Fälle		Fälle, in denen neben der Lues auch andere Krankheiten Anämie hervorrufen können
		An- zahl	%	
35—59	♂	3	2.9	Endocarditis lenta (1 Fall). Ulcus duodeni (1 Fall). Cirrhosis hepatis cum haematemeside (1 Fall)
60—69	♂	5	4.8	—
70—79	♂	7	6.7	Infectio rheumat. (1 Fall). Lymphomata colli (1 Fall). Helminthiasis (1 Fall)
80—84	♂	21	20.2	Ulcus ventr. (1 Fall). Helminthiasis (1 Fall)
≥ 85	♂	68	65.4	
35—59	♀	2	2.2	
60—69	♀	9	9.8	Lymphogranuloma inguinale (1 Fall). Venectasiae haemorrh. (1 Fall)
70—79	♀	26	28.3	
80—84	♀	23	25.0	
≥ 85	♀	32	34.7	

Tabelle 33.

Die Erythrozyten bei Späthues. Fälle 178 (♂ 99, ♀ 79).

Erythro- zyten Mill.	Ge- schlecht	Fälle		Fälle, in denen neben der Lues auch andere Krankheiten Anämie hervorrufen können
		An- zahl	%	
<3	♂	3	3.0	Endocarditis lenta (1 Fall). Cirrhosis hepatis cum haematemese (1 Fall)
3.0—3.999	♂	20	20.2	Lymphomata colli (1 Fall). Helminthiasis (2 Fälle). Nephropathia (1 Fall)
4.0—4.999	♂	40	40.4	Ulcus ventr. (1 Fall). Helminthiasis (4 Fälle)
≥4.5	♂	36	36.4	
<3	♀	1	1.3	
3.0—3.999	♀	36	45.6	Lymphogranuloma ing. (1 Fall). Ca ventr. (1 Fall). Venectasiae haemorrh. (1 Fall)
4.0—4.999	♀	22	27.8	
≥4.5	♀	20	25.3	

Tabelle 34.

Der Farbeindex (Hämoglobinwerte korrigiert) in den Anämiefällen (Hgb &lt; 85 % ♂ und 80 % ♀, E &lt; 4.5 Mill. ♂ und 4.0 Mill. ♀). Fälle 114.

Farbe- index	Fälle		Fälle, in denen neben der Lues auch andere Krankheiten Anämie hervorrufen können
	An- zahl	%	
<0.70	2	1.8	Ulcus duodeni (1 Fall)
0.70—0.89	7	6.1	Lymphogranuloma ing. (1 Fall). Cirrhosis hepatis cum haematemese (1 Fall)
0.90—1.10	82	72.0	Lymphomata colli (1 Fall). Venectasiae haemorrh. (1 Fall). Ulcus ventr. (1 Fall). Ca ventr. (1 Fall). Helminthiasis (5 Fälle)
1.11—1.20	20	17.5	Endocarditis lenta (1 Fall). Infectio rheumat. (1 Fall). Nephropathia (1 Fall). Helminthiasis (1 Fall)
1.21—1.30	3	2.6	

Tabelle 35.  
Die Leukozyten bei Spätlues. Fälle 175.

Leukozyten	Fälle	
	Anzahl	%
3000—3999 .....	11	6.3
4000—8000 .....	114	65.1
8001—10000 .....	35	20.0
>10000 .....	15	8.6

Tabelle 36.  
Die Variationsbreiten des normalen Blutbildes bei den Finnen.

Autor	Jahr	Ge- schlecht	Zahl der Unter- suchten	Hgb %	E (Mill.)	I
BECKER, G. <sup>1</sup> .....	1915	♂	22	93	5,510	0.99
		♀	18	84	4,730	0.99
APPELBERG, R. <sup>1</sup> .....	1919	♂	11	104	5,420	0.96
		♀	11	87	4,570	0.95
LINDSTRÖM, K. und TALL- QVIST, T. W. ....	1923	♂	35	95—105	4,800—5,320	0.91—1.05
		♀	35	80—90	4,410—4,690	0.90—1.02
FORSSELL, G. ....	1939	♂	10	73/85— 93/108	4,592—5,240	0.92—1.05
		♀	10	73/85— 85/98	4,032—5,388	0.89—1.05
TÖTTERMAN, G. ....	1939	♂	11	84/97— 93/108	4,608—5,232	0.98—1.06
		♀	11	73/85— 85/98	4,032—5,120	0.91—1.05

den Frauen 80 % und als normalen Erythrozytenwert bei den Männern mindestens 4.5 Mill. und bei den Frauen 4 Mill. je mm<sup>3</sup> betrachtet, so findet man bei meinen Spätluespatienten subnormale Hämoglobinwerte in 37.3 % und subnormale Erythrozytenwerte

<sup>1</sup> Die Angaben betreffen die Mittelwerte.



in 56.2 %. Subnormale Hämoglobinwerte kommen bei den Männern in 34.6 % und bei den Frauen in 40.3 % und subnormale Erythrozytenwerte bei den Männern in 63.6 % und bei den Frauen in 46.9 % vor. Die Werte sind nur leicht subnormal. Eine schwerere Anämie ist nur in 5 Fällen (2.6 %) anzutreffen. Bei einem Teil der an leichten Anämien und bei 3 an schweren Anämien Leidenden kann die Ursache auch in einer anderen Krankheit als der Lues bestehen.

Sieht man nach Tabelle 36 0.90—1.10 als normalen Farbeindex an, so sind von meinen *Anämiefällen* 72 % *normochrom*, 7.9 % *hypochrom* und 20.1 *hyperchrom*.

Mehrere Forscher erwähnen eine bei Spätluess vorkommende schwere hyperchrome Anämie (u. a. STRÜMPELL und SEYFARTH 1930, VESA 1930, FALLON 1938, TÖTTERMAN 1939). Andererseits kann man bei Lues eine schwere hypochrome (sekundäre) Anämie vorfinden (FOUCAR und STOKES 1921, HOFF 1924). Beiderlei schwere Anämien gelten als selten. Dagegen ist leichte Anämie bei Spätluess häufiger festzustellen (HOFF 1924, SCHULTEN 1939). Meine Ergebnisse stimmen demgemäss mit den Befunden anderer Forscher überein.

Wenn man als normale Leukozytenmenge 4000—8000 je mm<sup>3</sup> auffasst, besteht in meinem Material *Leukozytose* in 28.6 % und *Leukopenie* in 6.3 %. In dem Material von CLODI und MATUSCHKA (1924) war Leukozytose in 44 % festzustellen. Über spontane Leukopenie bei Lues hat in der Literatur, soviel ich sehe, MATABIKI (1907) berichtet.

Ich habe auch geprüft, ob in der Hämoglobinmenge sowohl bezüglich der Zahl der roten als der weissen Blutkörperchen ein auf der Art derluetischen Organveränderungen beruhender Unterschied nachzuweisen war. Indessen habe ich in dieser Hinsicht keine Abweichungen konstatieren können.

### *Die Senkungsreaktion der roten Blutkörperchen.*

Die meisten Forscher betrachten als normale obere Grenze der SR bei Männern 6—7 mm und bei Frauen 10—11 mm (u. a. FRISCH, KLEMPERER, WESTERGREN). Ich habe als solche Grenze bei beiden Geschlechtern 11 mm angenommen. Die Senkungsreaktion der

Erythrozyten bei den Spätluetpatienten meines Materials wird durch Abbildung 23 und 24 veranschaulicht. Danach war die SR in meinem Material in 85 % erhöht. Bei den Männern war dies in 82 % und bei den Frauen in 87 %, bei beiden Geschlechtern also mathematisch im gleichen Masse der Fall. In meinem ganzen

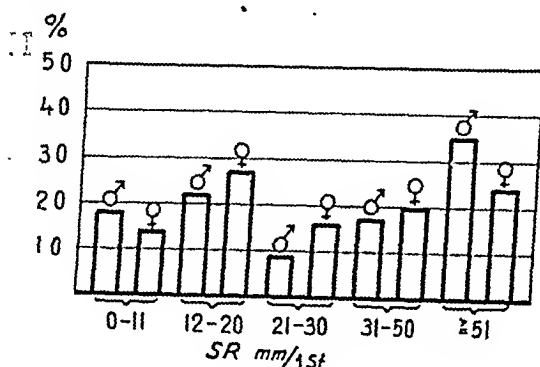


Abbildung 23. Die SR bei der Spätluet. Fälle 188 (♂ 102, ♀ 86).

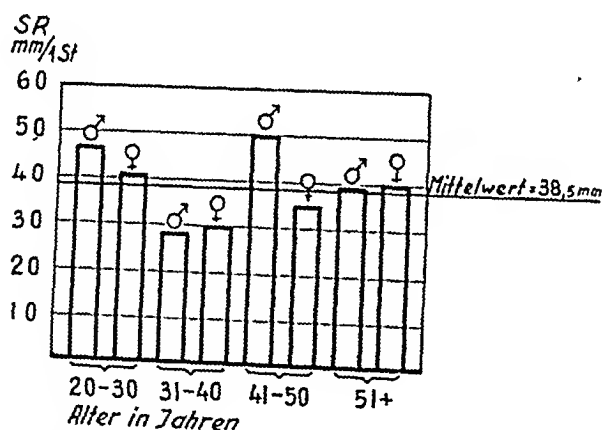


Abbildung 24. Die SR bei der Spätluet mit Rücksicht auf das Alter und Geschlecht der Patienten.

Material beträgt der Mittelwert der SR 38,5 mm. Soviel ich festgestellt habe, wirkt es auf die Höhe der SR nicht ein, an welcherlei Organlues der Patient leidet oder ob er überhaupt an einer manifesten solchen leidet. So findet man auch in schweren Fällen von Neuro- und Aortenlues neben hohen zugleich normale SR-Werte.

Ferner habe ich aus meinem Material 39 Fälle ausgesondert, bei denen ich keinen anderen zur Erhöhung der SR beitragenden Faktor als die Lues (keine andere Infektion, keine Blutkrank-

heiten, keine Nierenkrankheiten, keine Hypertonie, keine Arteriosklerose usw.) konstatieren konnte. Auch in diesen Fällen war die SR in 62 % erhöht, wobei ihr Mittelwert 24 mm in der Stunde, d. h. niedriger als der Mittelwert aller Fälle war. Mithin hat eine andere Krankheit steigernd auf die SR eingewirkt.

Nach den meisten Forschern ist die SR bei der Spätluës erhöht (u. a. BÜSCHER 1921, MAYR 1921, NATHAN und HEROLD 1921, FARBER und SCHULMAN 1925, PREININGER 1925), und zwar sowohl bei Viszeral- als bei Neuroluës bis zu 100 % (FARBER und SCHULMAN). Als Mittelwert der SR bei Spätluës geben NATHAN und HEROLD 14.5 mm (männliche Patienten) und PREININGER 35.6 mm an.

*In meinem Material hat das Alter der Patienten keinen Einfluss auf die Höhe der SR ausgeübt.* Nach manchen Forschern steigt die SR bei über 40jährigen an (LÖW-BEER 1929, BURKARDT 1930), während sie sich nach anderen nur unbedeutend oder gar nicht erhöht (MILLER 1936, NIEMI 1940).

### Andere spätluetische Krankheiten.

Die *Leberluës* ist in meinem Material spärlich vertreten. Sichere Fälle sind nur 6 (3 %) vorhanden. HJELMMAN hat bei uns (1892) unter 1860 Fällen von tertiärer Luës 32 (etwas unter 2 %) als Leberluës erkannt. Von KERPPOLA's (1937) 99 Ikterusfällen hatten diese Krankheit 3 (3 %). Die Angaben der ausländischen Autoren über die Frequenz der Leberluës weichen untereinander ziemlich stark ab, indem das Häufigkeitsprozent zwischen 16.5 und 4.2 schwankt (ROMBERG 1918, MELCHIOR 1922, LANGER 1926, NICKEL 1936).

*Diabetes mellitus* findet man in meinem Material bei 2 Patienten. Der eine von diesen bekam ausgiebige antiluetische Behandlung, doch besserte sich seine Zuckerkrankheit dadurch nicht. Der andere lehnte die antiluetische Therapie ab. In dem ersten Fall hat die Luës meines Erachtens wenigstens keinen beeinflussbaren Anteil an der Entstehung des Diabetes gehabt. Über den zweiten Fall lässt sich nichts sagen. In den 258 kombinierten Diabetes-Luës-fällen von McDANIEL, MARKS und JOSLIN (1940) war der Diabetes nach der Ansicht der Autoren in keinem einzigen Fall durch die Luës verursacht worden.

*Eiweiss* in kleinen Quantitäten mit oder ohne pathologisches Sediment, kam im Harn bei 5 Patienten vor. Es lässt sich in keinem Fall mit Sicherheit auf die Lues zurückführen, da in jedem komplizierende Krankheiten bestehen, und zwar in 2 Herzinsuffizienz, in 1 Sinuitis frontalis, in 1 Pyelonephritis und in 1 Polyarthrit.

Ohne näher auf die Fälle einzugehen, erwähne ich, dass von *Lungenlues* in meinem Material ein sicherer<sup>1</sup> und ein unsicherer Fall (1 %) vorliegen.

Luetische Nekrose im *Larynx* haben 2 Patienten und im *Pharynx* 1 Patient, was zusammen 1.5 % ausmacht.

Luetische *Iritis* ist bei 1, *Uveitis* bei 1 und *Chorioiditis* bei 3 Patienten, zusammen in 2.5 % zu finden. Eine *Atrophia nervi optici* zeigen 7 Patienten oder 3.5 %. Im ganzen weisen also 6 % luetische Augenerkrankungen auf.

Schliesslich sind 5 Fälle (2.5%) anzutreffen, in denen die *Müdigkeit*, von der nicht an einem luetischen Organfehler leidende Patienten belästigt wurden, durch spezifische Therapie verschwunden ist.

### Zusammenfassung über die Häufigkeit der spätluetischen Organveränderungen, verglichen mit ausländischen Untersuchungen.

In Tabelle 37 gebe ich eine Zusammenfassung über die Häufigkeit der wichtigsten Organveränderungen, die sich bei den Spätluetepatienten meines Materials entwickelt haben, und vergleiche sie mit den Befunden ausländischer Untersuchungen.

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<sup>1</sup> Der Fall ist von KAPLAN (Finska Läk. sällsk. Hdl. 81, 245 (1938)) veröffentlicht worden.

Tabelle 37.

	Mein Material %	Deutschland (und Österreich) %	U.S.A. %	Norwegen %	Dänemark %
Unkomplizierte Aortitiden .....	24.1	12.3—23.3 (STRELOW 1936, BRUINS 1916)	10.1—19.1 (TURNER 1930, KEMP und COCHUENS 1937, MAYNARD, Jr. 1935)	12.8 (BRUUS- GAARD (1929))	
Aortenklappeninsuffizienzen .....	14.1				
Aortenaneurysmen .....	7.5				
Systolische Hypertonie .....	27.1				
Neurolues mit schweren Liquorveränderungen	33.7	30.07—34.2 (NICKEL 1936, ROMBERG 1918, STRELOW 1936)	25.0—30.0 (MOORE, PARRAN 1937)	13.5 (GULDBERG 1932)	21.0 (MELCHIOR 1922)
Neurolues mit leichten	23.9				
Neurolues ohne Liquorveränderungen .....	3.6				
Leberlues .....	3.0	3.2—16.5 (NICKEL 1936, LANGER 1926, ROMBERG 1918)			9.0 (MELCHIOR 1922)
Blutveränderungen:					
1. SR erhöht (über 11 mm in 1 St.) .....	85.0				
2. Anämie:					
a) Hgb bei den Männern unter 85 % und bei den Frauen unter 80 % .....	37.3				
b) Erythrozyten bei den Männern unter 4.5 Mill. und bei den Frauen unter 4.6 Mill. ....	56.2				
3. Leukozytose (über 8,000 Leuk. je mm <sup>3</sup> ) ..	28.6	44.0 % (CLODI und MA- TUSCHKA 1924)			
4. Leukopenie (unter 4,000 Leuk. je mm <sup>3</sup> ) ..	6.3				

Die Neuro- und Aortenlues entwickeln sich demnach in Finnland in ausgedehnterem Masse als im Ausland. Nur 28 % meiner Luespatienten sind von Neuro- oder Aortenlues verschont geblieben.

Durch welche Ursache oder welche Ursachen dies bedingt ist, lässt sich schwer sagen. Bei meiner Untersuchung kann es sich nicht in höherem Grade um technische Fehler handeln. Es ist ja damit zu rechnen, dass mein Material nicht völlig mit demjenigen der anderen Autoren vergleichbar ist. Andererseits kann der Unterschied darauf beruhen, dass die anderswo untersuchten Materialien nur weit entwickelte Fälle von Organlues vertreten. Bei meinen Untersuchungen hinwieder ist intensiv nach asymptomatischer und beginnender Organlues gesucht worden. Eine Ursache könnte wohl auch darin liegen, dass sich die Luesimmunität in Finnland noch nicht in dem Grade entwickelt hat wie in anderen Ländern, die ihre Luesinfektion früher bekommen haben. Eine weitere Ursache kann sich in der Empfindlichkeit der Konstitution des finnischen Volkes verbergen. Als äussere Faktoren können ausserdem die Armut des finnischen Volkes und seine oft von Jugend auf schwere körperliche Arbeit gelten, die vielleicht dazu angetan sind, die Widerstandsfähigkeit herabzusetzen.

## Die Spezifität der serologischen Luesreaktion.

### Allgemeines.

Unter Unspezifität der Luesreaktionen versteht man bekanntlich, dass diese positiv sind, ohne dass der Betreffende an Lues leidet. Der Umschlag der positiven Reaktion in die negative ohne spezifische Therapie ist mitunter ein Zeichen, dass es sich um eine unspezifische Luesreaktion gehandelt hatte. Indessen ist es schwer, einen Fall ausschliesslich auf dieser Basis als unspezifisch einzuschätzen, denn, wie man weiss, kann ja auch die Reaktion von echtem Luesserum ohne spezifische Behandlung von der positiven in die negative übergehen.

Die Unspezifität der Luesreaktionen kann auf drei Umständen beruhen. Erstens auf *technischen Fehlern*. Zweitens auf den unbekannten Ursachen biologisch unrichtiger positiver Resultate bei *Gesunden*. Drittens können einige *Krankheiten* unrichtige

positive Reaktionsergebnisse hervorrufen. Die Wassermann-Reaktion findet man unspezifisch positiv bei akuten Infektionskrankheiten, besonders bei Pneumonie und Sepsis (Endocarditis lenta), Mononucleosis infectiosa, Framboesia, Trypanosomiasis, Febris recurrens, Lepra nodosa, Fleckfieber, Malaria tertiana, Diphtherie, bei Gravidität sowie manchmal auch bei Hauttuberkulose und nach Pockenimpfung (u. a. ELDH, FORSSMAN, MOORE, EAGLE und MOHR, LYNCH, BOYNTON und KIMBALL).

Manche Forscher begnügen sich bei der Beurteilung der Spezifität der positiven Luesreaktionen nicht mit einer Einteilung der Fälle in spezifische und unspezifische, sondern zerlegen sie in drei Gruppen: spezifische, wahrscheinlich spezifische und unspezifische (CUMMING, HAZEN, SANFORD, SENEAR, SIMPSON und VONDERLEHR 1935). Da es häufig auch sehr schwer ist, zu entscheiden, ob ein Fall spezifisch oder unspezifisch ist, weil er eine Mittelstellung einnimmt, ziehe auch ich bei der Behandlung diesen Umstand in Betracht.

### *Gruppierung der Reaktionsergebnisse.*

Hinsichtlich der Spezifität gruppieren ich die positiven (+) und suspekten (+ ?, ±, — ?) Reaktionsergebnisse in meinem Material wie folgt:

A. Spezifische, bei denen sicher Lues vorliegt.

B. Wahrscheinlich spezifische, bei denen es sich allem Anschein nach um Lues handelt.

C. Unspezifische, bei denen<sup>1</sup> man es unwahrscheinlicherweise mit Lues zu tun hat.

A. Als *spezifisch* betrachte ich die positiven und suspekten Reaktionen aus folgenden Gründen:

1. Wenn der Patient in der Anamnese Lues hat.

2. Wenn im Status des Patienten deutliche spätluetische Organveränderungen festzustellen sind. Im Bedarfsfall habe ich mich auf die Begutachtungen der Fachkliniken (der Abteilungen für Augen- sowie für Ohren-, Nasen- und Halskrankheiten) gestützt.

3. Wenn die Beschwerden des Patienten infolge von antiluetischer Behandlung aufgehört haben.

4. Wenn der Gatte bzw. die Gattin des Patienten an Lues leidet oder gelitten hat.

5. Wenn die Patientin ein vorzeitig gestorbenes Kind geboren hat.

6. Wenn der Patient Zeichen einer Lues im Sekundärstadium hat.

7. Wenn der Patient Zeichen kongenitaler Lues hat.

Bei manchen Patienten waren auch mehrere Umstände zu finden, auf Grund deren die Ergebnisse der Reaktion als spezifisch betrachtet werden können.

B. Als *wahrscheinlich spezifisch* fasse ich solche Reaktionen auf, die, mindestens zweimal untersucht, positiv waren, trotzdem die Anamnese keine Lues aufwies und auch im Status keine auf Lues deutenden Veränderungen gefunden wurden, aber nur in den Fällen, wo keine andere positive WR gebende Krankheit vorlag. Solche Fälle pflegt man im allgemeinen als sichere Luesfälle anzusehen (u. a. FORSSMAN, SIEVERS, VONDERLEHR, CLARK, WENGER und HELLER, Jr.).

C. Als *unspezifisch* betrachte ich solche Reaktionen, die bei wiederholter Untersuchung nur einmal ein positives oder suspektes Resultat gegeben haben und bei denen weder in der Anamnese noch im Status etwas mit Sicherheit auf Lues Deutendes zu finden ist. In manchen von diesen Fällen lag eine akute Infektionskrankheit vor.

### *Ergebnisse.*

In meinem Material finden sich:

A.	Sichere Luesfälle, in denen also die positiven und suspekten Resultate der Reaktionen spezifisch sind .....	201
B.	Wahrscheinlich sichere Luesfälle, in denen also die positiven Ergebnisse der Reaktionen allem Anschein nach spezifisch sind .....	19
C.	Unwahrscheinliche Luesfälle, in denen also die positiven und suspekten Resultate der Reaktionen offenbar unspezifisch sind .....	16

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Zusammen 236

#### *A. Sichere Luesfälle.*

1. 62 Fälle mit Lues in der Anamnese.
2. 107 Fälle mit deutlichen spätluetischen Veränderungen



hauptsächlich im Zentralnervensystem und in den Kreislauforganen, und zwar wie folgt:

a) 78 haben deutliche Symptome einer Neuroluet in Form von Pupillen- und Reflexstörungen sowie von Liquorveränderungen. Bei 48 dieser Fälle ist WR I oder WR II oder MBR II im Liquor positiv und bei 30 negativ. Von diesen Patienten leiden 30 überdies an Aortenlues und einer an Lues laryngis. Die Gatten zweier leiden an Lues.

b) 28 haben Aortitis oder Aortenaneurysmen oder Aortenklappeninsuffizienz ohne eine andere Ätiologie als Lues. Einer dieser Fälle leidet auch an Iritis luetica.

c) Ein Fall hat Ulcus lueticum pharyngis.

3. 6 Fälle, die, nach den Ergebnissen der antiluetischen Behandlung zu schliessen, als sichere Luesfälle betrachtet werden können. Bei 5 von diesen hat die Müdigkeit und bei einem der langwierige Husten mit Auswürfen nach antiluetischer Therapie aufgehört. Über Fälle der letzterwähnten Art finden sich Angaben im Schrifttum (CANNON).

4. 3 Fälle, in denen die Gatten an Lues gelitten haben.

5. 2 Fälle, in denen die Patientinnen Frühgeburten im VII—VIII Monat gehabt haben.

6. 13 Fälle kongenitaler Lues.

7. 8 Fälle sekundärer Lues.

B. *Wahrscheinlich sichere Luesfälle*, in denen also die positiven Ergebnisse der Reaktionen wahrscheinlich spezifisch sind.

19 Fälle, bei deren jedem die serologischen Luesreaktionen im Blute bei zweimaliger Untersuchung positiv waren. In der Anamnese hatte keiner Lues, wohl aber hatten 3 Ge und einer Ulcus molle. Einer war oft venerischer Infektion ausgesetzt. Im Status zeigte keiner einen Hinweis auf Lues.

C. *Unwahrscheinliche Luesfälle*, in denen also die positiven und suspekten Ergebnisse der Reaktionen offenbar *unspezifisch* sind.

Dieser sind es 16. Bei ihnen allen fanden sich nur in der ersten Blutprobe auf Lues deutende Blutveränderungen. In keinem Fall bestand in der Anamnese Lues. Auch war im Status von keinem etwas festzustellen, was mit Sicherheit für Lues sprach. Indessen lagen in 3 Fällen leichte Liquorveränderungen vor, die sich folgendermassen verhielten:

1. Pandy ++, Zellen 12.5/mm<sup>3</sup>, Mastixreaktion: 5,210,000,000, Goldsolreaktion: 221,000,000,000, WR —.

2. Pandy +, Zellen 6.3/mm<sup>3</sup>, Mastixreaktion: 1,000,000,000, Goldsolreaktion: 200,000,000,000, WR —.

3. Pandy +, Zellen 3.8/mm<sup>3</sup>, Mastixreaktion: 2,000,000,000, WR —.

Diese Liquorveränderungen können allerdings ebensogut von Lues wie von einer anderen Krankheit herrühren. Infolgedessen habe ich bei der Auffassung dieser Fälle als unspezifische einigermaßen willkürlich verfahren müssen.

Im folgenden führe ich die Ergebnisse der Blutreaktionen meiner unspezifischen Fälle sowie das Alter und die klinische Diagnose der Patienten an:

	Diagnose	Datum	WR I	WR II	KR	MBR
Fall 221; 29jähr. Arbeiter .....	Dyspepsia acida	20/8 36 31/10 36	± —	± —	+ —	+ —
• 222; 71jähr. Kleinbauer ....	Arterioscler. Emphysema pulm. Bronchitis chr. Myodeg. cordis	28/11 36 11/12 36 29/4 37	— — —	— — —	+ — —	— — —
• 223; 43jähr. » .....	Dyspepsia acida	3/2 37 12/2 37 23/2 37 27/10 37	— — — —	— — — —	+ — — —	— — — —
• 224; 55jähr. Arbeiter .....	Ca ventr. Anaemia hypo- chr.	12/2 37 7/3 37 20/4 37	— — —	— — —	+ — —	— — —
• 225; 29jähr. » .....	Infectio acuta	28/10 37 27/11 37	+ —	+ —	— —	— —
• 226; 16jähr. » .....	Bronchopneu- monia l. dx.	29/10 37 11/11 37 13/11 37	± — —	+ — —	+ — —	+ — —
• 227; 26jähr. Elektromonteur	Lupus vulgaris. Anaemia normo- chr.	11/11 37 13/11 37	— —	— —	— —	+? —

	Diagnose	Datum	WR I	WR II	KR	MBR II
Fall 228; 26jähr. Drechsler .....	Bronchitis ac.	29/12 37 31/12 37 7/4 38	— — —	— — —	— — —	+ — —
» 229; 23jähr. Aufwartefrau ..	Enteritis ac.	19/8 36 7/9 36 11/9 36	+ — —	+ — —	+ — —	+ — —
» 230; 64jähr. Hofbäuerin ....	Dyspepsia. Hypertonia	19/8 36 9/9 36 18/9 36 2/1 37	+ — — —	+ — — —	+ — — —	+ — — —
» 231; 53jähr. Arbeiterfrau ....	Dyspepsia. Hypertonia. Myodeg., in- suff. cordis	16/6 37 1/6 38 3/6 38	— — —	— — —	+? — —	— — —
» 232; 30jähr. Fräulein .....	Polyarthrit. ac. (gonorrhoeica?)	31/8 37 24/9 37 3/1 38	— — —	— — —	— — —	+ — —
» 233; 29jähr. Arbeiterfrau ....	Graviditas m. IV	6/9 37 27/11 37	— —	— —	— —	+ —
» 234; 56jähr. Kleinbauer ....	Hypertonia. Helminthiasis. Anaemia levis	4/12 37 31/1 38	— —	— —	— —	+? —
» 235; 20jähr. Anstreicher ....	Bronchitis ac. Helminthiasis. Anaemia normo- chr.	8/12 37 13/12 37 6/6 38 25/6 38	— — — —	— — — —	— — — —	+? — — —
» 236; 30jähr. Arbeiter .....	Lupus vulgaris. Helminthiasis. Anaemia normochr.	18/12 37 5/5 38 21/5 38 29/6 38	— — — —	— — — —	— — — —	+ — — —

Unter den positiven und suspekten Ergebnissen der Wassermann-Reaktionen finden sich zusammen 5 offenbar unspezifische. Die klinischen Diagnosen dieser Fälle sind: Dyspepsia acida, Infectio ac., Bronchopneumonia, Enteritis ac., Dyspepsia acida et hypertonia.

Die positive und suspekthe Kahn-Reaktion ist 8 mal unspezifisch, und zwar einmal bei chronischer Bronchitis, 2 mal bei Dyspepsie, einmal bei Carcinoma ventriculi, einmal bei Bronchopneumonie, einmal bei Enteritis acuta und 2 mal bei Hypertonie mit Dyspepsie.

Die positive und suspekthe MBR II ist 11 mal unspezifisch: 5 mal bei einer akuten Infektionskrankheit, 2 mal bei Lupus vulgaris, einmal bei Dyspepsie, einmal bei Dyspepsie mit Hypertonie, einmal bei Hypertonie mit Helminthiasis und einmal bei Gravidität.

*Bei den an akuten Infektionskrankheiten Leidenden haben mithin in meinem Material am meisten bei den Luesreaktionen unspezifisch positive und suspekthe Resultate vorgelegen.*

Im Obigen habe ich gezeigt, in welchem Masse die positiven und suspekten serologischen Luesreaktionen unspezifisch gewesen sind. Als zu empfindlich können die von mir angewandten Luesreaktionen im Blute auf der anderen Seite kaum betrachtet werden, denn sie haben mitunter ein schwach positives, ja die gleichen Fälle bisweilen ein negatives Resultat gegeben, obwohl die Patienten an schweren luetischen Läsionen im Zentralnervensystem und an Aortenfehlern gelitten haben. Im folgenden führe ich 3 solche Fälle aus meiner Kasuistik an.

*Fall 113. L.: L. 36jährige Arbeiterfrau.*

Dg.: Aortitis. Lues cerebrospinalis. Struma.

Anamnese: 2 Jahre lang Kopfschmerzen und Nervosität.

St. pr. (11. 10. 1937): Schilddrüse vergrößert und knotig. Über der Aorta ein systolisches Geräusch. Zweiter Aortenton akzentuiert und metallisch. Aorta röntgenologisch deutlich erweitert. Pupillen deform, reagieren nicht auf Licht.

Blut (15. 9. 36): WR I —, WR II —, KR —, MBR II —.

» (11. 10. 37): WR I —, WR II +, KR ±, MBR II ±.

Lumbalflüssigkeit: Pandy +, Nonne +, Zellen 106.0/mm<sup>3</sup>, WR I 1.0 cm<sup>3</sup> +, WR I 0.5 cm<sup>3</sup> +, MBR II +, Mastixreaktion: 5,200,000,000, Goldsolreaktion: 432,000,000,000.

D. m.: Pat. bekam Malariafieber- und antiluetische Therapie. Das Befinden besserte sich. Zugenommen. Kopfschmerzen und Nervosität aufgehört.

*Fall 126. Selma H. 55jährige Arbeiterfrau.*

Dg.: Arteriosclerosis. Hypertonia. Myodeg. et insuff. cordis. Lues cerebrospinalis. Anaemia hypochromica levis.

Anamnese: 2 Monate Atemnot.

St. pr. (17. 6. 37): Art. radialis geschlängelt. Über dem Herzen ein systolisches Geräusch. Zweiter Aortenton akzentuiert. RR 170/105 mm Hg. Nervensystem o. B.

Blut (17. 6. 37): WR I —, WR II —, KR +, MBR II —.

(8. 7. 37): WR I —, WR II —, KR —?, MBR II —.

Lumbalflüssigkeit: Pandy +, Nonne +, Zellen 23.0/mm<sup>3</sup>, WR II 1.0 cm<sup>3</sup> —, MBR II +, Mastixreaktion: 3,320,000,000, Goldsolreaktion: 243,330,000,000.

Fall 131. Anna P. 52jährige Landwirtsfrau.

Dg.: Lues cerebrospinalis.

Anamnese: 3 Kinder totgeboren. 2 Jahre lang Bauchbeschwerden und Kreuzschmerz. Während dieser Zeit stark abgemagert. Ein Jahr lang Schwindel und Kopfschmerz.

St. pr. (12. 9. 37): Pat. bleibt nicht aufrecht stehen. Patellarreflexe erloschen. Babinski +. Bei dem Nabel ein handtellerbreites Gebiet, in dem die Schmerzempfindung herabgesetzt ist. Pupillen gross, deform, verengern sich nicht auf Licht, wohl aber auf Entfernung.

Blut (12. 9. 37): WR I —, WR II —?, KR +, MBR II —.

Lumbalflüssigkeit: Pandy +, Nonne schwach +, Zellen 16.0/mm<sup>3</sup>, WR I 1.0 cm<sup>3</sup> ±, WR I 0.5 cm<sup>3</sup> ±, WR II 1.0 cm<sup>3</sup> +, WR II 0.5 cm<sup>3</sup> +, MBR II +, Mastixreaktion: 5,210,000,000.

D. m.: Pat. hat Malariafieber- und antiluetische Therapie bekommen. Das Befinden hat sich gebessert. Kopfschmerz und Schwindel haben aufgehört. Im Lauf von 2 ½ Jahren 19 kg zugenommen.

Aus den Tabellen 38 und 39 wird ersichtlich, in welchen Prozentsätzen die positiven und suspekten Ergebnisse der Luesreaktionen unspezifisch oder unsicher (wahrscheinlich spezifisch) sind.

Tabelle 38.

Das Unspezifitätsprozent der positiven (+) Luesreaktionen in dem untersuchten Material.

Reaktion	Die den Kontrolluntersuchten entsprechende Patientenzahl	Zahl der positiven (+) Ergebnisse	Unspezifisch		Unsicher (wahrsch. spezif.)	
			Anzahl	%	Anzahl	%
WR I .....	6,752	135	3	0.04	13	0.19
WR II ....	6,834	156	4	0.06	15	0.22
KR .....	6,272	209	7	0.11	18	0.29
MBR II ....	5,292	164	8	0.15	17	0.32

Tabelle 39.

Die Unspezifität der suspekten (+?,  $\pm$ , —?) Luesreaktionen in dem untersuchten Material.

Reaktion	Die den Kontrolluntersuchten entsprechende Patientenzahl	Zahl der suspekten (+?, $\pm$ , —?) Ergebnisse	Unspezifisch		Unsicher (wahrsch. spezif.)	
			Anzahl	%	Anzahl	%
WR I .....	7,302	27	2	0,03	3	0,04
WR II ....	7,213	27	1	0,01	2	0,03
KR .....	9,104	6	1	0,01	—	—
MBR II ....	4,574	11	3	0,07	—	—

Da sich nicht alle Patienten, bei denen die Luesreaktionen im Blute positiv oder suspekt waren, zur Kontrolluntersuchung eingefunden haben, berechne ich das Unspezifitäts- und Unsicherheitsprozent der Reaktionen nur aus der prozentualen Menge, die den zur Kontrolluntersuchung gekommenen Patienten entspricht. Beispielsweise folgendermassen: unter den 10,953 untersuchten Patienten war die WR I bei 219 positiv. Von diesen erschienen 135 zur Kontrolluntersuchung. Alsdann ist die diesen 135 Nachuntersuchten entsprechende ursprüngliche Patientenmenge, bei der die WR I ermittelt wurde, x Patienten.

Nun ist  $219:135 = 10,953:x$ ,

also  $x = 6,752$ .

Ferner ist in meinem Material die positive WR I unspezifisch in 3 Fällen, mithin in Prozenten:

$$\begin{aligned} 6,752 &= 100 \% \\ 3 &= y \% \\ y &= 0,04 \%. \end{aligned}$$

Die WR I ist folglich in meinem Material unspezifisch positiv in 0,04 %.

Wie man aus den Tabellen 38 und 39 sieht, gibt die WR I unspezifisch positive Resultate in 0,04 %, WR II in 0,06 %, KR in 0,11 % und MBR II in 0,15 %. Ausserdem sind von den positiven Ergebnissen unsicher, aber wahrscheinlich mit Hinweis auf Lues: WR I

Tabelle  
Die Unspezifität der Luesreaktionen. Vergleich

Autor	Jahr	Untersuchungsort	Art des Materials	Umfang des Materials
ELDN, S. ....	1932	Schweden, Sahlgren- sehes Krankenhaus	Pat. eines Kran- kenhauses f. in- nere Medizin	17,108
FORSSMAN, J. ....	1932	Schweden, medizinische Klinik der Univ. Lund	Pat. eines Kran- kenhauses f. in- nere Medizin	7,711
KALLNER, S. ....	1939	Schweden, medizinische Polikl. des Serafimer- lazarets	Pat. eines Kran- kenhauses f. in- nere Medizin	7,550
STRENG, OSV., SIE- VERS, O., VUORI, A. K.	1933	Serobakt. Institut der Univ. Helsinki	Verschiedene	?
TURUNEN, A. ....	1935	I. Univers.-Frauenkl. in Helsinki	Schwangere	5,092
HONKANEN, A. ....	1936	Tub.-Krankenhaus in Helsinki	Pat. eines Tub.- Krankenhauses	611
SIEVERS, O. ....	1937	Serobakt. Institut der Univ. Helsinki	Verschiedene	?
MAIJALA, P. ....	1942	Medizinische Polikl. des Allgem. Krankenhauses in Helsinki	Pat. einer medi- zinischen Polikl.	4,480- 9,104

in 0.19 %, WR II in 0.22 %, KR in 0.29 % und MBR II in 0.32 %. In den suspekten Ergebnissen der verschiedenen Reaktionen schwankt die Unspezifität und Unsicherheit zwischen 0.01 und 0.07 %.

In Tabelle 40 sind die Unspezifitätsergebnisse der Luesreaktionen bei den in Schweden und in Finnland ausgeführten Untersuchungen miteinander verglichen. In den Materialien der schwedischen Forscher sind die Unspezifitätsprozente niedrig und so ziemlich gleich den meinigen.

40.

der Ergebnisse einiger Autoren.

Unspezifität der positiven (+) Luesreaktionen %				Unspezifität der suspekten (+?, ±, —?) Luesreaktionen %			
WR I	WR II	KR	MBR II	WR I	WR II	KR	MBR II
ca. 0.3							
0.065	0.065	0.065					
0.13		0.13	0.13				
0.5		1.0					
0.75		0.75					
		0.66					
0.57	0.78	1.48	1.47	0.04	0.08	0.08	0.71
0.04 <sup>1</sup> (0.19)	0.06 <sup>1</sup> (0.22)	0.11 <sup>1</sup> (0.29)	0.15 <sup>1</sup> (0.32)	0.03 <sup>1</sup> (0.04)	0.01 <sup>1</sup> (0.03)	0.01	0.07

*Zusammenfassung.*

Ich habe gefunden, dass die Unspezifität der Luesreaktionen in meinem Material ausserordentlich gering ist. Gering würde sie auch in dem Falle bleiben, wenn man die unsicheren Fälle zu den Unspezifischen zählen würde. Dieses Ergebnis dürfte darauf beruhen, dass ich eine genaue klinische Untersuchungsmethodik angewandt habe, zu der eine röntgenologische Untersuchung der Aorta sowie eine Untersuchung der Zerebrospinalflüssigkeit gehörten. Mit

<sup>1</sup> Prozentzahlen der unsicheren Fälle (wahrsch. spezif.).



dieser Untersuchungsmethode sind von den seropositiven, als asymptomatisch zu betrachtenden luetischen Erkrankungen der Aorta und des Zentralnervensystems möglichst viele diagnostiziert worden. Der geringe Grad der Unspezifität dürfte auch durch die Beschaffenheit des Materials bedingt sein, welches sich hauptsächlich aus Fällen von *chronischen* inneren Krankheiten zusammensetzt. Als übermässig empfindlich dürfte die in dieser Arbeit angewandte Technik für die Untersuchung der Luesreaktionen meines Erachtens nicht anzusehen sein.

## ZUSAMMENFASSUNG.

Der Zweck der vorliegenden Arbeit ist, weiteres Licht über folgende Fragen zu verbreiten:

1. In welchem Masse kommt bei uns in Finnland seropositive Spätluës vor?

2. In welchem Umfang entwickeln sich heutzutage in unbehandelten und mangelhaft behandelten Luësfällen Veränderungen in den inneren Organen und von welcher Art sind diese Veränderungen in Finnland?

3. Da in der Diagnostik der Luës heutzutage grossenteils empfindliche serologische Methoden zur Anwendung kommen, ist es meines Erachtens von Wichtigkeit, auch genauer festzustellen, inwieweit die gewöhnlichsten in Finnland gebräuchlichen serologischen Reaktionen der Luës zuverlässig sind.

Bei 10,954 Patienten der medizinischen Poliklinik des Allgemeinen Krankenhauses (Universitätskliniken) in Helsinki wurden die WR I, WR II, KR und MBR II untersucht. Die Prüfung der Reaktionen erfolgte im Serobakteriologischen Institut der Universität Helsinki und ist fast durchgängig von Dozent OLOF SIEVERS ausgeführt worden.

Bei 401 Patienten war eine der vorerwähnten Reaktionen positiv oder suspekt. Alle diese Fälle verwende ich bei der Behandlung der Frage von der Häufigkeit der Luës.

236 der erwähnten 401 Patienten kamen zu meiner genaueren klinischen Kontrolluntersuchung. Diese Fälle berücksichtige ich bei der Erörterung der Frage nach der Spezifität der Luësreaktionen.

Von den genannten 236 Patienten litten an sekundärer Luës 8, an kongenitaler Luës 13 und an sicherer oder wahrscheinlich

sicherer Spätluetes 199. Die Spätluetefälle verwende ich bei der Behandlung der auf die Organluetes bezüglichen Fragen. Bei den übrigen 16 Patienten waren die positiven bzw. suspekten Luesreaktionen unspezifisch.

WR I gab unspezifische Ergebnisse in 0.04 %,

WR II » » » » 0.06 %,

KR » » » » 0.11 %,

MBR II » » » » 0.15 %.

WR I-positive und -suspekte Lues wurde in dem Material insgesamt in 2.5 % angetroffen<sup>1</sup>,

WR II-positive und -suspekte Lues wurde in dem Material insgesamt in 2.78 % angetroffen<sup>1</sup>,

KR-positive und -suspekte Lues wurde in dem Material insgesamt in 3.28 % angetroffen<sup>1</sup>,

MBR II-positive und -suspekte Lues wurde in dem Material insgesamt in 3.1 % angetroffen<sup>1</sup>.

Irgendeine dieser Reaktionen trat in dem Material in 3.44 % auf<sup>1</sup>.

Die Männer hatten etwa 1.3 mal mehr Lues als die Frauen.

65.8 % der männlichen und 73.6 % der weiblichen Luetiker gaben zu, dass sie nicht von ihrer Krankheit gewusst hatten.

6 der Patienten mit Spätluetes hatten vollständige und 38 unvollständige antiluetische Therapie erhalten.

155 der Patienten mit Spätluetes hatten keine antiluetische Behandlung erhalten.

Bei den an Spätluetes leidenden Patienten kamen Veränderungen in der Aorta und im Zentralnervensystem in bedeutendem Masse vor.

Aortenfehler waren insgesamt in 45.7 % festzustellen. Von diesen waren unkomplizierte Aortitiden 24.1 %, Aortenklappeninsuffizienzen 14.1 % und Aneurysmen 7.5 %. Aneurysmen wurden bei den Männern mehr als bei den Frauen angetroffen. Der durchschnittliche Blutdruck war bei den Spätluetetikern erhöht. Systolische Hypertonie wurde in 27.1 % gefunden.

Eine wichtige Feststellung war die Symptomenarmut der unkomplizierten Aortitiden. Jeder zweite der Aortitispatienten hatte

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<sup>1</sup> Das Unspezifitätsprozent abgezogen.

keine auf eine Erkrankung der Kreislauforgane hinweisende subjektive Beschwerden. Wenn eine unkomplizierte Aortitis Beschwerden auslöste, bestanden dieselben vorzugsweise in präkordialen Schmerzen. Die komplizierten Aortenprozesse haben dagegen in beachtlichem Masse subjektive Beschwerden verursacht, die sich besonders in Atemnot und stenokardischen Schmerzen äusserten.

Bei den unkomplizierten Aortitiden war die Aorta in 27 % nicht erweitert. In den Obduktionsfällen wurde trotzdem eine schwere Aortitis konstatiert. Im Ekg war die Strecke ST bei den Aortitiden in 73 % erniedrigt.

Neurolues kam im ganzen in 61.2 % vor. Sie trat bei den Männern und Frauen im gleichen Masse auf. Die meisten Fälle von Neurolues waren Encephalomyelitisfälle. Klassische Tabes und Paralyse fanden sich ausserordentlich spärlich. Von den Neuroluesfällen waren 15.2 % asymptomatischer Natur.

Die Spätluespatienten zeigten subnormale Hämoglobinwerte in 37.3 %, subnormale Erythrozytenwerte in 56.2 %, Leukozytose in 28.6 % und Leukopenie in 6.3 %. Die SR war in 85 % erhöht. Der Mittelwert der SR betrug 38.5 mm. Das Alter der Patienten schien keinen Einfluss auf die Höhe der SR zu haben.

Leber-, Lungen-, Larynx- und Pharynxlues kamen selten vor. Luetische Augenaffektionen waren etwas häufiger zu finden.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CXXXVII

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## DAS VORKOMMEN UND DIE VERBREITUNG DER MULTIPLEN SKLEROSE IN SCHWEDEN

ZUR GEOGRAPHISCHEN PATHOLOGIE DER  
MULTIPLEN SKLEROSE

VON

*THOR SÄLLSTRÖM*

# ACTA MEDICA SCANDINAVICA

(SUB TITULO

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# DAS VORKOMMEN UND DIE VERBREITUNG DER MULTIPLEN SKLEROSE IN SCHWEDEN

Zur geographischen Pathologie der  
multiplen Sklerose

von

THOR SÄLLSTRÖM

STOCKHOLM 1942

STOCKHOLM 1942.  
STOCKHOLMS BOKINDUSTRI' AKTIEBOLAG

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## Einleitung.

Die geographische Pathologie hat während der letzten Jahrzehnte zweifellos in immer stärkerem Masse die Aufmerksamkeit auf sich gelenkt; eine grosse Anzahl von Arbeiten wurden auf diesem Forschungsgebiet veröffentlicht und auch in Schweden sind einige grössere Untersuchungen vorgelegt worden. Trotzdem muss man feststellen, dass verschiedene Meinungen über die Bedeutung dieser Art von Pathologie herrschen. Dies ergab sich auch deutlich als ich neulich ein kurzes Referat über die vorläufigen Ergebnisse der vorliegenden Arbeit anlässlich einer Tagung der schwedischen Pathologenvereinigung hielt. Diese Ansicht ist verständlich, wenn man bedenkt, mit welcher grossen Schwierigkeiten und Fehlerquellen die geographische Pathologie zu kämpfen hat, und wenn man berücksichtigt, dass in den weitaus meisten Fällen beachtliche Bedenken gegen ihre Methoden und das behandelte Material gerichtet werden können. Derjenige, der nicht tiefer in sie eingedrungen ist, kann also leicht zu der Auffassung kommen, dass dieser Forschungszweig wertlos sei. Und doch hat die geographische Pathologie einige augenscheinliche Ergebnisse erzielt. Erwähnt sei hier nur die Forschung in den Problemen der Struma, der Thyreotoxikose und der pernisiösen Anämia. Über das Vorkommen dieser Krankheiten verdanken wir der geographischen Pathologie Klarheit schaffende Angaben. Unzweifelhaft ist weiter, dass die verschiedenen Volksstämme sehr ungleich auf die unterschiedlichen Krankheiten reagieren. —

Während der Arbeit an meiner früheren Untersuchung über das Vorkommen der Thyreotoxikose in Schweden wurde bei mir ein grosses Interesse für die geographische Pathologie und ihre Bedeutung begründet, und es war mein Wunsch nach Vollen-  
dung dieser Arbeit eine ähnliche neue Untersuchung durchzuführen, um Kontroll- und Vergleichsmaterial für die frühere Abhandlung zu erhalten. In Übereinstimmung mit Professor *Folke Henschen*, der mir bei meiner Arbeit über das Vorkommen der Thyreotoxikose in Schweden behilflich gewesen war,

und nach Besprechungen mit den Professoren *Viktor Wigert* und *Nils Antoni* wurde als Gegenstand der neuen Untersuchung das *Vorkommen der multiplen Sklerose in Schweden* gewählt. Die Gründe für diese Wahl waren in der Hauptsache folgende: die multiple Sklerose ist hierzulande eine keineswegs seltene Krankheit, weiter ist sie klinisch und pathologisch hentzutage siemlich gut abgrenzbar und schliesslich muss man auf Grund früherer Untersuchungen im Auslande den Eindruck gewinnen, dass eine geographisch-pathologische Studie gerade dieses Leidens zu wertvollen Ergebnissen führen könnte.

Als ich diese neue geographisch-pathologische Untersuchung begann, war ich mir der sich bietenden grossen Schwierigkeiten durchaus bewusst. Trotz dem erwiesen sich dieselben während der Arbeit als wesentlich grösser; insbesondere waren sie mit denen meiner früheren Untersuchungen über das Vorkommen der Thyreotoxikose nicht vergleichbar und teilweise ganz anderer Natur. Nunmehr — nach fünfjähriger Arbeit — bin ich aber doch soweit gelangt, dass ich die Ergebnisse vorlegen kann.

Eine besondere Freude bereitet es mir, dadurch die Gelegenheit zu erhalten, Herrn *Professor Henschen* für sein grosses Interesse und die wertvolle Hilfe zu danken, die er mir bei der Planung der Untersuchung zuteil werden liess.

Bei der Sammlung des Materials haben mir die Lizentiaten der Medizin *Gösta Fallénius* und *Yngve Holmstedt*, sowie Herr cand. med. *Sven Sällström* wertvolle Hilfe geleistet. Auch ihnen möchte ich an dieser Stelle wärmstens danken.

Dank schulde ich allen Krankenhausärzten Schwedens, die mir ihr Material an multipler Sklerose freundlichst zur Verfügung gestellt haben, sowie auch der grossen Zahl von Provinzialärzten, die liebenswürdigerweise meinen an sie gerichteten Fragebogen über das Vorkommen der multiplen Sklerose ausführlich beantwortet haben.

Schliesslich ist es mir eine angenehme Pflicht, der »*Stiftelsen Thérèse och Johan Anderssons Minne*« für wertvolle pekuniäre Hilfe meinen ergebendsten Dank auszusprechen.

Bei der Übersetzung ins Deutsche war mir Herr Stadtverwaltungsrat *K. Bölsche* liebenswürdigerweise behilflich.

# I. Kapitel.

## A. Der Begriff der multiplen Sklerose.

Die multiple Sklerose ist schon lange als Krankheit erkannt. Bereits 1848 wird sie in *Cruveilhiers* Arbeit erwähnt. Genauer bekannt wurde sie jedoch erst durch *Charcot's* grundlegende Arbeit 1868. *Charcot* war der erste, der den charakteristischen histologischen Anfall der Krankheitsherde im Nervensystem bei der multiplen Sklerose beschrieb. Seitdem ist die multiple Sklerose in einer Menge von Schriften behandelt worden; von verschiedenen Gesichtspunkten her wurde sie erforscht und schliesslich wurde mit fortschreitender Erkenntnis ein sehr grosses Variabilität im klinischen Bild der Krankheit erkannt. Auf diese Weise ist man nunmehr zu der Auffassung gekommen, dass die multiple Sklerose eine der gewöhnlichsten Erkrankungen im Nervensystem ist.

Zugleich mit einer derartigen Ausweitung des Krankheitsbegriffes musste man sich aber darüber im klaren sein, dass die Abgrenzung der multiplen Sklerose wesentlich schwerer geworden war. Das charakteristische Bild der Krankheit, wie es *Charcot* beschrieb und das durch die nach ihm benannte Trias: Nystagmus, skandierendes Sprechen und Intentionstremor gekennzeichnet wurde, findet man nunmehr nur in einer geringen Anzahl von Fällen der multiplen Sklerose.

In den Anfangsstadien ist die Diagnose oft sehr schwer. Nicht selten machen die Patienten den Eindruck als litten sie an Neurasthenie, Hysterie oder Rheumatismus. Gewöhnlicher ist aber, dass die Krankheit mit ein Teil oft flüchtigen Symptomen beginnt: heispielweise Neuritis optica — und zwar in Form vorübergehender Amanrosis oder zentraler Skotome —, Diplopien, Facialisparesen, spastische Paresen in den Beinen, Blasenstörungen

und Ataxie. Das häufigste und bedeutungsvollste dieser Symptome ist ohne Zweifel Neuritis optica.

Das voll entwickelte Bild der multiplen Sklerose bietet gewöhnlich eine besonders grosse Fülle verschiedener Symptome, die aus den verschiedenen Teilen des Nervensystems hergeleitet werden können und von Fall zu Fall — oft auch von Zeit zu Zeit im gleichen Fall — wechseln. Manches Mal wird man sich über den Einzelfall erst auf Grund der weiteren Krankheitsentwicklung ein Urteil bilden können, und es bedarf mitunter einer langwierigen Beobachtung des Patienten, um zur Diagnose zu kommen.

Wenn man versuchen wollte, das Charakteristische der multiplen Sklerose anzuzeigen, so müssen in erster Linie drei Punkte hervorgehoben werden: 1.) Voransgehende oft flüchtige Krankheitssymptome, die viele Jahre bevor das eigentliche ernsthafte Bild der multiplen Sklerose sich entwickeln können. 2.) Ein polymorph klinisches Bild, das auf Grund charakteristischer pathologisch-anatomischer Veränderungen im Nervensystem entsteht. 3.) Die Tendenz der Krankheit zu Remissionen mit unter sogar zu Intermissionen. Das Bild der multiplen Sklerose wird von diesen drei Hauptgruppen von Symptomen insgesamt gebildet.

Die Diagnose wird im Kapitel über die Beschaffung des Materials zum Gegenstand einer eingehenderen Besprechung.

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### *B. Das Wissen über das Vorkommen und die Verbreitung der multiplen Sklerose.*

Das Vorkommen der multiplen Sklerose war Gegenstand zahlreicher Untersuchungen, von denen einige schon vor dreissig bis vierzig Jahren durchgeführt wurden. Diese verschiedenen Untersuchungen können aber nicht unmittelbar miteinander verglichen werden, weil leider die Untersuchungsmethoden stark von einander abweichen. So wird beispielsweise in einem Teil der Fälle die Zahl der an multiple Sklerose erkrankten Patienten im Verhältnis zu den übrigen gleichzeitig behandelten Nerven-

fällen angegeben, in anderen Fällen sind sie zur Anzahl aller behandelten Patienten in Relation gesetzt, in wieder anderen Fällen wurden sie zu einer bestimmten Volksmenge in Beziehung gesetzt. Der grösste Nachteil der meisten Publikationen auf diesem Gebiet muss aber darin erblickt werden, dass das Material von nur irgend einer einzelnen Klinik herangezogen wird und dass dann das Vorkommen im Verhältnis zu dem Umkreis studiert wird, von dem angenommen wird, dass ihn diese Klinik umspanne. Hierdurch sind sicherlich fehlerhafte Schlüsse z. B. mit Bezug auf die Verteilung der Krankheit unter Land- und Stadtbewohnern und innerhalb gewisser Berufsgruppen entstanden. Ein Teil der Untersuchungen wurde bei Militärpflichtigen durchgeführt, wobei man als Fehlerquelle in Rechnung ziehen muss, dass alle Untersuchten sich in einem Alter befinden, in dem die multiple Sklerose am gewöhnlichsten ist. Nur in einer geringen Anzahl Arbeiten wurden grössere oder kleinere Gruppen eines ganzen Volkes studiert. Wenn diese Untersuchungen also auch nicht voll vergleichbar sind, so enthalten sie doch Vieles, das von bedeutenden Wert und grossem Interesse ist.

Im grossen gesehen kann man sagen, dass *Steiner* die Verhältnisse in Europa dahin zusammenfasst, dass die multiple Sklerose in den nördlichen Staaten Europas also in Skandinavien, England, Gross-Deutschland, Nord- und Zentralfrankreich, den Niederlanden, Belgien und der Schweiz gewöhnlicherweise vorkomme. Die Krankheit wäre dagegen ungewöhnlich in Südeuropa d. h. in Italien, Spanien, Rumänien sowie entlang der Mittelmeerküste Frankreichs. Umfangreichere Untersuchungen der europäischen Verhältnisse sind nur in Dänemark, Deutschland, England und der Schweiz vorgenommen.

In Dänemark führte *Gram* eine Untersuchung über die Lokalisation der Fälle durch, die bei den Krankenversicherungsgesellschaften angemeldet worden waren, d. h. also der Fälle, die Invaliditätshilfe bekamen. Er fand, dass die multiple Sklerose in einer Zone, die die Mitte der Halbinsel Jütland und die Insel Fünen umfasst häufiger anzutreffen war als nördlich des Limfjord, südlich des Kongeflusses und östlich des Grossen Belt, wo sie seltener auftrat. Ganz selten war sie auf Bornholm.



In Deutschland wies *Müller* schon 1904 darauf hin, dass die multiple Sklerose eine gewöhnliche Nervenkrankheit wäre und dass ihre Frequenz sicherlich diejenige der Syringomyelien und der Lues cerebrospinalis überträfe, ja möglicherweise die der Tabes dorsalis erreiche. Dass die Krankheit nicht ungewöhnlich war, geht auch daraus hervor, dass *Max Borst* — worauf *Bing* im gleichen Jahre hinweist — in seiner 1904 herausgegebenen Monographie über die multiple Sklerose über nicht weniger als 252 deutsche Arbeiten referiert, gegenüber nur 82 französischen. 1932 schätzte *Marburg* die Anzahl der Fälle von multipler Sklerose auf 10 % aller Nervenfälle und 1938 gab *Schaltenbrand* die entsprechende Ziffer mit ca 8 %. Eine Totalzahl aller Krankheitsfälle in Deutschland findet sich nirgends, aber *Schaltenbrand* berechnet die Frequenz auf etwa 1 pro Mille der Bevölkerung. Danach ist die Krankheit recht gewöhnlich in Deutschland. Die Ausbreitung der multiplen Sklerose über das ganze Land ist auch deutlichen regionären Wandlungen unterworfen. *Toss* studierte das Vorkommen der multiplen Sklerose in verschiedenen Kliniken Deutschlands und fand, dass, wenn man 5 Kliniken des östlichen Deutschlands mit ebenso vielen des westlichen vergleicht, man in Ostdeutschland 137 Fälle und in Westdeutschland 403 Fälle der Erkrankung feststellt. Er vertritt die Ansicht, dass der Unterschied so in die Augen fallend wäre, dass für ihn eine Ursache lokaler, klimatischer, sozialer oder rassenbiologischer Art gefunden werden müssen. Vergleichsweise erfragte er auch die Verhältnisse in Dorpat und fand dort ebenfalls eine niedrigere Frequenz der Krankheit.

Zusammenfassend kann man also sagen, dass die multiple Sklerose oft in Deutschland vorkommt und zwar mehr in seinen westlichen als in den östlichen Teilen.

Was England betrifft, so finden wir zunächst eine Untersuchung von *Bramwell*. Er berechnet die durchschnittliche Lebensdauer der Patienten mit multipler Sklerose auf 8 Jahre und schätzte gestützt auf diese Ziffer und den jährlichen Todesprozentsatz das Vorkommen der multiplen Sklerose bei den lebenden Personen Englands einschliesslich Wales auf 160 Fällen für 1 Million Individuen. *Wilson* berechnete die Mortalität für jede Grafschaft in England für das Jahr 1925 und fand sie für das

ganze Land mit 17,5 per 1 Million Einwohner. Die Frequenz variierte indessen höchst bedeutend für die verschiedenen Grafschaften. So hatte beispielsweise der Gerichtsbezirk von Peterborough eine Todesziffer von 103,3 per Million, während in den Grafschaften Meddlesex, Dorset und Buckingham die Ziffer unter 9 per Million betrug. *Russel Brain* legte 1930 eine Statistik von The Hospital for Epilepsy and Paralysis in London vor, die 5 Jahresperioden 1924—28 umfasste, und auf Grund deren er feststellte, dass in diesem Nervenmaterial die multiple Sklerose etwa 8 % ausmachte. Diese Ziffer stimmt mit der von *Schaltenbrand* für Deutschland gefundenen gut überein. *Russel Brain* zeigt auch auf, dass bei der multiplen Sklerose jährlich ca. 760 Todesfälle in England vorkommen, was ungefähr 20 auf 1 Million Einwohner bedeutet.

Eine Untersuchung von teilweise anderer Art ist die, die *Allison* 1929 über die Verhältnisse in Nordwales machte. Er sammelte mit Hilfe aller Aerzte das gesamte Material an multipler Sklerose in einem Bezirk von Nordwales, untersuchte die verschiedenen Fälle selber und studierte deren verschiedene Verhältnisse insbesondere Lokalisation, Alter, Beruf usw. Er fand auf diese Weise 71 sichere Fälle von multipler Sklerose und zwar diffus verteilt über den gesamten untersuchten Bezirk, der 489 000 Einwohner umfasste.

Das Land, das bisher die besten statistischen Untersuchungen über das Vorkommen der multiplen Sklerose besitzt, ist die Schweiz. Dort legten *Bing* und *Reese* 1926 eine Arbeit über die multiple Sklerose in der Nordwestschweiz vor und *Ackermann* setzte 1931 die Statistik über das ganze Land fort. *Bing* und *Reese* gingen bei ihrer Untersuchung derart zu Werke, dass sie vom Eidgenössischen Gesundheitsamt einen Fragebogen an alle Aerzte der zu untersuchenden Gebiete versenden liessen. In der Enquête fürden die einzelnen Aerzte über die Zahl der von ihnen während der Jahre 1918—1922 behandelten Fälle von multipler Sklerose befragt; Aufschluss wurde auch über die hauptsächlichsten Symptome dieser Fälle begehrt, sowie Angaben über die übrigen Umstände z. B. Alter, Beruf, Geschlecht, Wohnung. Zugleich mit der Herausgabe der Fragebogen erschien in der *Revue Médicinal de la Suisse Romande* ein aus-

gezeichneter orientierender Artikel über multiple Sklerose. Auf diese Weise erhielten die Verfasser für die Nordwestschweiz 281 Fälle. Nach sorgfältiger Durchsicht des Materials stellten sie fest, dass es durchaus zuverlässig war. *Ackermann* dehnte dann diese Untersuchung über die ganze Schweiz aus und erhielt so zusammen 610 Fälle von multipler Sklerose. Das entsprach einer Morbiditätsziffer von 1,96 auf 10 000, berechnet im Verhältnis zur Volksmenge (3 108 000) der Schweiz für 1930. Am meisten betroffen war der Kanton Zürich mit 3,9 auf 10 000. Beim Studium der Frequenzkarte, die *Ackermann* veröffentlichte, nimmt man wahr, dass die Frequenz auffällig grösser im nördlichen Teil als im südlichen ist. Allerdings findet man im Alpental Moesa, das in der Südschweiz liegt, eine stärkere Frequenz; doch kann dies ein Zufall sein, denn es handelt sich nur um 5 Fälle auf etwas mehr als 6 000 Einwohner.

Zusammenfassend kann man feststellen, dass ein auffälliger Unterschied zwischen der nördlichen und der südlichen Schweiz besteht, wobei die Frequenz im Norden erkennbar grösser ist.

Von den übrigen Teilen Europas gibt es nur vereinzelte geringe Statistiken. Als solche wird man die von *Voss* gemachte Angabe auffassen müssen, dass er während der ganzen langen Zeit seiner siebenjährigen Arbeit an der Nervenklinik in St. Petersburg nur einige vereinzelte Fälle von multipler Sklerose beobachtet habe.

*Kreindler* meldet 86 Fälle aus Rumänien (1934), *Marinesco* gibt an, dass die Krankheit in Rumänien ungewöhnlich sei. Und *Borreguero* sagt das gleiche für die Lage in Spanien. Nach *Guilain* sind die Mittelmeerländer im Vergleich zu Mittel- und Nordeuropa relativ verschont.

In Amerika wurde früher angenommen, dass die multiple Sklerose recht ungewöhnlich wäre. Zuerst wurde dies von *Smith* 1904 hervorgehoben, der seine Untersuchungsergebnisse aus den USA, mit den Angaben verglich, die *Bramwell* als den englischen Anteil errechnet hatte. Auch *Bramwell* hatte die Ansicht vertreten, dass die multiple Sklerose in England viel gewöhnlicher sei als in den USA. 1922 stellte *Wechsler* 1970 Fälle von multipler Sklerose zusammen, von denen er 1773 aus der Literatur zusammengelesen, den Rest selbst studiert hatte. Er

glaubte sich in der Lage aufweisen zu können, dass die multiple Sklerose, die früher recht ungewöhnlich in den USA. gewesen sei, nun häufiger geworden wäre. Er verglich daher bei seinem zusammengestellten Material die Verhältnisse in den USA. mit denjenigen in Europa und kam zu dem Ergebnis, dass die europäischen Angaben eine Durchschnittsfrequenz von 1,33. % zuließen, während die amerikanische Statistik diese Ziffer mit 0,36 % gab.

Im selben Jahr — 1922 — veröffentlichte *Davenport* eine grosse Arbeit über die geographische Verbreitung der multiplen Sklerose. *Davenport* untersuchte das Vorkommen der Krankheit an Hand der ärztlichen Untersuchungen der während des früheren Weltkrieges eingezogenen Männer und fand, dass die höchste Ziffer 18 auf 100 000 Individuen gewesen. Man muss sich bei dieser Angabe allerdings bewusst sein, dass das Material, das *Davenport* sich auf solche Weise beschafft hatte, ja nur das männliche Geschlecht betrifft und dass es gerade die Altersgruppen behandelt, bei denen die multiple Sklerose am gewöhnlichsten vorkommt. Das Verhältnis der von der Gesamtbevölkerung der USA. an multipler Sklerose erkrankten Bevölkerung dürfte nicht höher als 5 auf 100 000 sein. *Davenport* fand eine deutliche geographische Verschiedenheit hinsichtlich der Verbreitung der Krankheit. Die höchsten Ziffern seines Materials wurden in Michigan, Minnesota, Wisconsin und in Staaten, die an die grossen Seen grenzen, gefunden. Ausserhalb dieser Gebiete ergaben die höchsten Ziffern die Staaten Washington, Mississippi und Maine. Aber man kann auf die Detailstudien solcher Untersuchung nicht allzuviel Gewicht legen, weil sie ja nur eine verhältnismässig geringe Anzahl von Fällen umfasst. Dennoch wird man zusammenfassend behaupten dürfen, dass diese Untersuchung erwiesen hat, dass ein bemerkenswerter Unterschied zwischen den nördlichen und den südlichen Teilen der USA. dergestalt besteht, dass die multiple Sklerose gewöhnlicher in den Norddistrikten, ungewöhnlicher in den südlichen ist.

Um das Vorkommen der Krankheit in den übrigen Teilen der Welt beurteilen zu können, stehen nur vereinzelte publizierte Angaben zur Verfügung. Nach einer Mitteilung bei *Steiner* ist

die multiple Sklerose selten in Brasilien und nach *Russel Brain* auch in Chile. *Russel Brain* und *Kooy* geben an, dass sie sehr ungewöhnlich in Südafrika sei, aber in Ostafrika von *Fischer* beobachtet wurde. *Stender* teilt mit, dass die Krankheit in Madagaskar und in Aegypten unbekannt wäre.

Was Asien angeht, so wird die multiple Sklerose von *Miura* und *Pfister* als in Japan und China zu den Seltenheiten gehörig angesehen. Dieselbe Auffassung wird von *Wood* für den Chinesischen Teil, von *Okhuma* und *Stender* für den Japanischen Teil vertreten. *Wood's Arbeit* erschien 1929 und bestand aus einer Studie über das Material der neurologischen Kliniken in China. Er berechnete das Vorkommen der multiplen Sklerose teils im Verhältnis zu den neurologischen Fällen, und zwar mit 150 zu 100 000, was 0,15 % entspricht, teils im Verhältnis zu den gewöhnlichen Erkrankungen mit 75 zu 100 000. Er hätte nur zwei klassische Fälle gesehen und in der chinesischen Litteratur keinen Fall gefunden, von dem man annehmen könnte, dass er zu dieser Krankheitsgruppe gehöre. Keinerlei anatomische Untersuchungen waren gemacht worden.

*Cuthbert Sprawson* arbeitete zwei Jahre lang in Mesopotamien und danach in Britisch Indien und fand während dieser Zeit zwei Fälle bei Europäern und keinen bei Eingeborenen. In Kalkutta wurden einige typische Fälle unter den Eingeborenen festgestellt. Im Pundschab ein Fall bei einem Indoeuropäer, in Bengalen 10 Fälle, von denen 2 Europäer betrafen. *Verhaart* hat im Zeitraum von 5 Jahren 11 Fälle von multipler Sklerose in Batavia beobachtet. In der Nervenklinik dort findet man etwa 100 Kranke jährlich und der davon entfallende Prozentsatz beläuft sich auf 0,24 %, eine sehr niedrige Ziffer.

*Beringer* beobachtete in Burjat-Mongul in russisch Sibirien südlich des Baikalsees relativ oft multiple Sklerose.

Schliesslich gibt *Stender* an, dass auf Island die multiple Sklerose gewöhnlicher als Lues sei.

Wenn man in Kürze das zusammenzufassen versucht, was über das Vorkommen und die Ausbreitung der multiplen Sklerose bekannt ist, so kann man im Grossen gesagt werden, dass die Krankheit sowohl in Europa, wie in den USA. ziemlich gewöhnlich ist, doch häufiger in Europa als in Nordamerika vor-

kommt. In beiden Erdteilen ist der nördliche Raum am meisten betroffen. Wie *Steiner* es ausdrückt, ist die multiple Sklerose in Europa unter 40 Grad nördlicher Breite sehr selten und in den USA. unter 30 Grad. In den übrigen Teilen der Erde ist die Krankheit selten, doch wird ihr Vorkommen sowohl aus Südamerika und Südafrika gemeldet, wie aus Asien.

Es versteht sich von selbst, dass man durch die vereinzelter Untersuchungen, die über die Verbreitung und das Vorkommen der multiplen Sklerose angestellt wurden, nur ein sehr unsicheres und unvollständiges Bild erhalten kann. Die gesundheitspflegerische Wirksamkeit und die Stellung der Bevölkerung der Ärzten gegenüber dürfte auch recht verschieden an den verschiedenen Stellen der Erde sein, was bedeutet dass die Angaben, die von so vielen verschiedenen Plätzen kommen, mit grosser Unterschiedlichkeit beurteilt werden müssen. Trotzdem hat es den Anschein, als ob bei den Untersuchungen, die bisher in dieser interessanten Frage zu Stande gekommen sind, geographische Verschiedenheiten im Vorkommen der Krankheit gefunden worden wären.

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## 2. Kapitel "Das Material".

### 1. *Die Beschaffung des Materials.*

In derselben Weise, wie bei meiner Untersuchung über das Vorkommen der Thyreotoxikose in Schweden habe ich mir für die multiple Sklerose Material von den verschiedenen Krankenhäusern des Landes verschafft. Wenn man eine geographisch-pathologische Studie wie die vorliegende beabsichtigt, kann es keinem Zweifel unterliegen, dass die Beschaffenheit des Materials von entscheidender Bedeutung ist. Und zwar kommt es nicht nur darauf an, dass die eingesammelten Fälle eine richtige Diagnose aufweisen, sondern von mindestens gleicher Bedeutung ist es, dass das eingesammelte Material im Hinblick auf das relative Vorkommen innerhalb der verschiedenen Distrikte homogen bleibt. Die multiple Sklerose gehört zu den Krankheiten, die in grösstem Ausmass die Patienten ins Krankenhaus führt. Die oft sehr invalidisierenden Symptome erschrecken die Patienten und veranlassen sie ärztliche Hilfe aufzusuchen. Das Krankenhausmaterial der Krankheit muss daher die meisten an multipler Sklerose Erkrankten umschliessen.

Trotzdem finden sich natürlich nicht alle Fälle der Krankheit in Krankenhäusern. Ein Teil wird zu Hause behandelt, andere sind vielleicht zufälligerweise in irgend eine Heilstätte gelegt worden. Dass es sich hierbei aber keineswegs um eine grössere Anzahl von Fällen handelt, geht aus einer Umfrage hervor, die ich an sämtliche Provinzialärzte des Landes richtete und über die ich weiter unten noch berichten werde. Aus den Antworten auf diese Umfrage kann man nämlich entnehmen, dass diese Ärzte sogar wie ausnahmslos Fälle, die sie im Verdacht der multiplen Sklerose haben oder

bei denen multiple Sklerose vermutet wird, ins Krankenhaus senden. Sonach kann man voraussetzen, dass die allermeisten Fälle von multipler Sklerose irgendwann einem Krankenhaus zugeführt werden, um richtig diagnostiziert zu werden. Ein Material, das aus dem Krankenhausmaterial der verschiedenen Krankenhäuser des Landes hergeleitet wird, dürfte deshalb den grössten Teil der Fälle von multipler Sklerose umfassen, die während der Untersuchungsperiode an der Krankheit erkrankt sind. Bei meiner Untersuchung der multiplen Sklerose, die im Jahr 1935 in Angriff genommen wurde, habe ich das Krankenhausmaterial der zehnjährigen Periode von 1925 bis 1934 gewählt. Der Grund, warum ich gerade diese Periode wählte, ist zunächst darin zu sehen, dass ich es für notwendig hielt, bis zum Jahre 1925 zurückzugehen, um hinreichend grosses Material zu erhalten, weiter aber auch darin, dass ich mich bei meiner vorhergegangenen Untersuchung der Thyreotoxikose der gleichen Periode bediente und dergestalt in dem Thyreotoxikosematerial eine Kontrolle erhalten konnte für die hier angewandte Untersuchungsmethode.

Eine vorläufige Angabe über das Vorkommen der multiplen Sklerose im Lande kann man aus den Jahresberichten erhalten, die die verschiedenen Krankenhäuser an die Königl. Medizinalverwaltung erstatten. In der Tabelle 1 habe ich die Ziffern der Jahresberichte zusammengestellt.

Gestützt auf diese Tabelle habe ich dann bei Besuchen der verschiedenen Krankenhäuser mich nach den berichteten Fällen von multipler Sklerose umgesehen und vollständige Journalabschriften derselben gemacht. Bei dieser meiner sehr zeitraubenden und kostspieligen Arbeit hatte ich eine wertvolle Hilfe durch die Lizentiaten der Medizin Gösta Fallén und Yngve Holmstedt, sowie durch meinen Bruder den Kandidaten der Medizin Sven Sällström.

Das gesammelte Material, das zusammengefasst aus 3641 Journalabschriften bestand, wurde karteimässig registriert und in alphabetische Reihenfolge gebracht. Hierbei zeigte sich, dass eine sehr grosse Anzahl Patienten im Register mehrere Male geführt worden waren, denn ein Teil dieser Patienten war mehrere Male im selben Krankenhaus behandelt worden, ein Teil hatte



Krankenhaus	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	Summe
Seraphimerlaz.	26	29	30	36	30	21	43	35	32	55	337
Sabbatsberg	4	5	4	2	2	5	1	0	2	4	29
St Göran	0	0	0	1	1	1	1	6	0	3	13
St Erik	8	8	9	13	7	12	21	20	12	13	123
Martin	3	3	5	5	2	2	0	2	3	2	29
Asa	4	4	2	4	6	5	4	4	3	1	36
Mörlby	4	3	7	11	7	6	5	0	3	0	46
Löwenström	1	1	0	0	2	1	2	4	3	0	14
Söderålfje	1	0	0	0	1	3	0	3	1	2	11
Norrålfje	0	0	1	0	1	3	1	0	1	1	8
Östhammar	1	0	0	0	0	0	1	1	2	2	7
Uppsala	17	19	24	25	28	41	18	31	31	24	258
Nyköpings	0	2	2	2	0	2	2	4	4	0	16
Ekstisrum	1	0	1	1	2	2	0	14	7	12	40
Elen	0	0	0	0	1	0	0	0	0	0	2
Katrineholm	1	0	0	1	1	0	0	1	0	0	4
Linköping	3	8	9	12	8	17	4	10	18	16	105
Söderköping	0	0	1	1	0	0	2	2	1	0	8
Vadstena	0	0	1	1	0	0	1	1	2	6	6
Finspång	0	0	1	3	4	3	4	1	1	1	18
Kisa	1	0	0	0	0	0	0	0	0	1	2
Norrköping	0	1	8	4	4	5	5	0	3	18	28
Jönköping	2	2	13	19	11	10	10	10	3	18	98
Ekso	0	0	0	0	0	0	1	0	0	2	3
Värnamo	0	0	1	3	0	2	3	0	0	3	12
Vaxjö	3	2	1	0	2	2	2	2	5	5	24
Ljunghy	2	3	2	2	4	0	1	2	1	0	17
Västervik	3	1	2	0	2	0	3	4	1	3	25
Kalmar	1	3	3	0	0	8	2	2	1	0	3
Oskarshamn	0	1	0	0	0	0	0	0	0	0	5
Borgholm	0	0	0	0	0	0	0	0	0	0	0

Tabelle 1. Die Frequenz der multiplen Sklerose in den Krankenhäusern während der Jahre 1925—1934 auf Grund der der Königl. Medizinalverwaltung erstatteten Jahresberichte. Es muss bemerkt werden, dass die Ziffern in dieser Tabelle sehr irreführend sind und keineswegs die tatsächliche Lage entsprechen. Eine grosse Anzahl Patienten sind zwei oder mehrere Male im selben Krankenhaus behandelt worden, und sie sind jedesmal in den Jahresberichten an die Königl. Medizinalverwaltung als neue Fälle registriert worden, wodurch die Zahl der meldeten Fällen zu gross geworden sind. Eine ausführliche Beschreibung über diese Tabelle findet sich in den Kapiteln II und III statt.

Krankenhaus	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	Summe
Visby	0	0	0	1	0	0	0	0	0	0	1
Karlskrona	2	0	2	3	2	0	3	0	4	4	20
Karlshamn	3	1	6	7	6	8	3	0	1	1	36
Kristianstad	2	3	8	6	8	6	3	3	14	18	71
Simrishamn	1	3	2	0	2	0	3	1	0	3	15
Ängelholm	0	0	0	0	0	1	1	1	0	4	7
Lund	32	22	29	28	28	26	35	37	38	43	318
Landskrona	1	1	0	0	1	2	1	0	3	0	9
Hälsingborg	7	6	6	6	3	10	7	5	4	6	60
Ystad	0	0	1	1	3	1	3	2	0	0	11
Trelleborg	0	0	1	2	1	0	2	3	1	1	11
Hörby	1	0	2	2	0	3	1	1	0	0	10
Malmö	7	5	5	13	7	6	10	7	10	3	73
Halmstad	0	3	6	3	3	1	5	5	4	4	34
Falkenberg	1	0	0	1	2	0	0	0	0	0	4
Varberg	1	0	3	3	2	2	3	3	4	4	25
Kungälv	0	0	0	0	1	0	0	1	0	0	2
Uddevalle	1	3	2	3	2	3	17	13	10	1	55
Strömstad	0	1	1	3	3	0	3	1	0	0	12
Mölnådal	0	2	1	1	0	0	0	1	1	0	6
Sahlgren	24	26	40	25	29	36	16	9	18	17	240
Vänersborg	2	5	2	6	5	5	13	12	13	11	74
Alingsås	1	3	2	0	2	2	6	2	1	2	21
Borås	1	0	3	2	3	11	9	12	20	17	78
Mariestad	3	0	0	0	2	1	1	3	0	1	11
Lidköping	2	4	2	4	2	5	2	25	44	51	141
Falköping	6	1	2	4	0	4	4	2	3	4	30
Karlstad	9	12	26	13	16	22	19	16	6	22	161
Filipstad	0	0	0	1	0	0	1	0	0	1	3
Torsby	2	1	0	1	2	4	0	0	2	2	14
Ärjäng	0	1	0	2	1	1	0	1	1	5	12
Örebro	3	10	8	7	14	16	17	15	13	13	115
Västerås	0	0	1	4	14	12	8	6	8	10	63
Sala	0	1	0	0	0	0	0	0	3	2	6
Köping	0	0	0	0	0	1	0	0	0	0	1
Norberg	0	1	0	1	0	1	0	1	1	1	6
Falun	6	3	8	13	7	14	11	8	7	5	82
Avesta	0	0	1	2	0	0	1	1	0	1	6
Mora	2	0	0	0	0	2	1	1	0	0	6
Smedjebacken	0	0	0	0	0	0	0	0	0	0	0
Ludvika	1	3	1	1	1	0	0	0	1	1	9
Gävle	1	2	4	2	4	8	7	11	8	9	56
Söderhamn	1	3	3	2	1	1	2	0	2	1	16

Krankenhaus	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	Summe
Hudiksvall	1	0	0	0	1	0	1	1	0	0	4
Bollnäs	0	0	2	0	1	0	0	0	0	1	4
Härnösand	0	0	1	0	0	0	0	0	1	1	3
Sundsvall	1	1	1	0	2	5	2	2	10	0	24
Örnsköldsvik	0	4	0	0	3	5	5	5	2	3	27
Backe	1	0	0	0	0	0	0	0	1	0	2
Sollefteå	2	0	0	0	0	1	0	1	1	0	5
Östersund	2	2	1	1	0	2	9	7	5	9	38
Sveg	0	1	1	1	1	0	1	1	0	1	7
Umeå	1	10	11	25	17	16	24	19	6	14	143
Skellefteå	1	2	1	4	3	2	2	3	11	4	33
Luleå	0	1	0	0	0	0	2	0	0	0	3
Piteå	0	0	0	0	0	0	0	0	1	1	2
Haparanda	1	1	0	0	0	1	0	0	0	0	3
Gällivare	2	0	1	2	3	2	1	6	1	0	18
Eksjö	0	0	4	2	2	0	2	2	4	0	16
Sollefteå garn.	0	0	1	0	5	0	0	0	0	1	7
Boden	0	0	0	0	3	5	6	0	5	7	26
	221	245	330	357	345	404	409	418	431	481	3641

in mehreren verschiedenen Krankenhäusern gelegen. In der Tabelle 2 habe ich die Ziffern, die diese Verhältnisse beleuchten zusammengestellt.

Auf diese Weise wird die Anzahl der der Königl. Medizinalverwaltung angegebenen Fälle um mehr als 30 % verringert. Wahrscheinlich dürfte diese Ziffer noch höher sein, denn in einigen Krankenhäusern sind die Patienten, die zwei- oder mehrmals während desselben Jahres eingelegen haben, im Jahresbericht als ebensovielen verschiedenen Fällen angegeben worden. Demgegenüber ist in der Tabelle jeder Fall nur als ein Fall gerechnet worden, auch wenn über ihn mehrere Journale gefunden wurden.

In einer geringen Zahl von Fällen — etwa bei 30—40 — konnten Journaleintragen nicht festgestellt werden.

Durch all diese verschiedenen Umstände wird mein Material weiter vermindert und es verbleibt schliesslich eine totale Anzahl von 2100 Fällen.

Tabelle 2. Die Tabelle zeigt, wie die der Königl. Medizinalverwaltung berichteten Fälle dadurch vermindert werden, dass sie mehrfach im selben oder in verschiedenen Krankenhäusern behandelt wurden.

Anzahl der Behandlungsperioden im selben Krankenhaus	2	3	4	5	6	7	8	9	Summe
Die tatsächliche Zahl der Patienten	339	143	44	35	10	0	1	1	573
Die Zahl der geführten Journalfälle	678	429	176	175	60	0	8	9	1535
Anzahl der Aufenthalte in verschiedenen Krankenhäusern	2	3	4	5	6	7	8	9	Summe
Die tatsächliche Zahl der Patienten	211	35	5	0	0	0	0	0	251
Die Zahl der geführten Journalfälle	422	105	20	0	0	0	0	0	547

Im Anschluss an diese Feststellungen sind dann die Journale eingehend durchstudiert und die verschiedenen Fälle beurteilt worden. Bei einer Krankheit, wie der multiplen Sklerose ist es selbstverständlich, dass viele Fälle unsicher sind. Ich war gezwungen aus dem vorliegenden Material nicht weniger als 735 Fälle als unsicher auszumerken, also etwa 30 % aller Fälle. Mit Rücksicht diese grosse Zahl unsicherer Fälle habe ich es für notwendig gehalten in einem späteren Kapitel gerade diesen Teil des Materials noch ausführlicher zu behandeln. Bei 1365 Fällen wird angenommen, dass sie ein einigermaßen sicheres Bild der multiplen Sklerose darbieten. Die Prinzipien für deren Beurteilung und eine ausführliche Darlegung der hauptsächlichsten Symptomkomplexe bei diesen Fällen werden im folgenden Kapitel gegeben.

An sämtliche Fälle, die sicheren sowohl wie die unsicheren, wurde nunmehr ein Frageformular folgender Fassung herausgesandt:

1. Wo und wann sind Sie geboren?

Wie lange wohnten Sie am Geburtsort?

Sind Sie von dort verzogen?

Wo haben Sie seitdem gewohnt und wie lange an jedem Platz — Angabe der Jahreszahl erbeten?

2. Wann stellten Sie erstmalig fest, dass Sie diese Nervenkrankheit hatten?

Waren Sie vorher immer gesund gewesen?

Wo wohnten Sie als die Krankheit begann?

Wie lange waren Sie zu dieser Zeit schon dort ansässig?

3. Wie bemerkten Sie zuerst, dass Sie krank waren?

Kamen die Krankheitsbeschwerden plötzlich oder suchten Sie auf Grund langsamer Verschlimmerung das Krankenhaus um Hilfe auf? Waren Ihre Beschwerden während der ganzen Zeit gleich schwere oder hatten Sie gewissen Perioden mit fühlbarer Verbesserung?

4. Wenn ja, wie lange waren in solchem Fall im allgemeinen die Krankheitsperioden und wie lange waren Sie dann besser?

Haben die Krankheitsbeschwerden vor vielen Jahren begonnen und waren sie dann während langer Zeit ungefähr die gleichen, um sich plötzlich zu verschlimmern?

5. Gibt es in Ihrer Verwandtschaft jemanden, der an derselben Nervenkrankheit wie Sie leidet oder litt?

In welchem Verwandtschaftsverhältnis steht er zu Ihnen?

Gibt es in Ihrer Umgebung (Nachbarn, Bekannte usw.) jemanden, der an derselben Krankheit leidet oder litt?

Gibt es in Ihrer Verwandtschaft jemanden, der an Tuberkulose, Struma, geistiger Zurückgebliebenheit, Hirntumor oder einer anderen Gehirn- oder Nervenkrankheit leidet?

6. Waren Ihre Eltern miteinander verwandt?

Wenn ja, in welchem Verwandtschaftsverhältnis standen Sie zueinander?

Welchen Beruf (welche Beschäftigung) hatten Ihre Eltern?

7. Haben Sie selbst eine der nachfolgenden Krankheiten gehabt? (Um Angabe der Jahreszahl, wann Sie erkrankten wird gebeten):

Lungentuberkulose?

Andere Arten der Tuberkulose?

Erythema nodosum (»knölnros«)?

Gelenkrheumatismus?

Gehirnhautentzündung?

Haben Sie andere Krankheiten gehabt?

Haben Sie als Waffenträger gedient oder geübt?

8. Was hatten Sie im Jahre vor Ihrer Erkrankung für einen Beruf?  
 Worin bestand Ihre Arbeit?  
 Waren Sie ausserhalb des Hauses beschäftigt?  
 Waren Sie innerhalb des Hauses beschäftigt?  
 Wie war der Arbeitsplatz gelegen?  
 Haben Sie stets dieselbe Arbeit oder denselben Beruf gehabt?  
 Wann wechselten Sie den Beruf?  
 Welcher Art waren Ihre Lebensumstände im Jahre vor Ihrer Erkrankung?  
 Wie war Ihre Wohnung gelegen?
9. Hatten Sie während der Zeit, die Ihrer Erkrankung voraus ging,  
 etwas mit Haustieren zu tun?  
 Haben Sie an der Pflege von Tieren teilgenommen?  
 Hatten Sie selbst Tiere?  
 Haben Sie kranke Tiere gepflegt?
10. Worin erblicken Sie selbst die Ursache Ihrer Krankheit?

Diese Korrespondenz war sehr zeitraubend. Die ersten Briefe wurden Anfang 1936 versandt und die letzten Antworten kamen im November 1941 herein. Eine ziemlich grosse Anzahl Patienten waren während dieser 10 jährigen Zeitspanne nicht einmal sondern mehrmals verzogen. Daher war ich gezwungen den Anschriften von mehreren hundert Fällen in Pastoraten und Meldeämtern nachzugehen. In einer bestimmten Zahl von Fällen konnten keine Angaben erlangt werden, weil die in Frage stehenden Patienten einige Zeit nach ihrem Krankenhausaufenthalt verstorben waren. In recht vielen dieser Fälle konnte ich die Patienten allerdings durch Rückfragen bei den entsprechenden Pastoraten lokalisieren. Alles in Allem erhielt ich auf meine Rundfrage 1384 Antworten, d. h. also, dass etwa 66 % des gesamten Patientenmaterials (2100 Fälle) sich geäussert haben. 369 dieser Antworten betrafen die unsicheren und 1015 die sicheren Fälle. In Prozenten antworteten demnach etwa 66 % der unsicheren und etwa 75 % der sicheren Fälle. Diese letzt genannte Ziffer entspricht genau der, die ich bei meiner Untersuchung der Thyreotoxikose im Lande erhielt. Angaben über die Verhältnisse von Patienten in geographischer Hinsicht konnten in 155 Fällen in den Pastoraten erlangt werden. Nur in 195 Fällen habe ich nicht die geringste Antwort erhalten.

Diese Patienten konnten auch in Pastoraten oder Meldeämtern unter den in den Journalen angegebenen Anschriften nicht ermittelt werden. Auf Grund der Antworten des Fragebogens konnte das Material weiter verringert werden, denn in 5 weiblichen Fällen hatten sich die Patientinnen zwischen zwei verschiedenen Krankenhausaufenthalten verheiratet und waren infolge des Namenswechsels in der Kartei als zwei verschiedene Fälle aufgenommen worden.

Das Verschicken des Fragebogens zeigte sich von grosser Bedeutung für die Lokalisierung der Patienten innerhalb des Landes. Eine Untersuchung, die sich lediglich auf die in den Journalen angegebenen Anschriften gestützt hätte, würde sicherlich sehr unzuverlässig und irreführend geblieben sein. In einer keineswegs geringen Anzahl von Fällen hatten die Patienten nämlich im Journal die zufällige Anschrift eines Verwandten oder Bekannten in der Stadt, in der sich das Krankenhaus befand, angegeben, während ihre eigene Anschrift eine ganz andere war. In einem Teil anderer Fälle waren die Patienten erst kürzlich an die im Journal angegebene Stelle umgezogen und waren an einem ganz anderen Ort erkrankt. Für die multiple Sklerose ist es charakteristisch, dass lange Zeit, ja manchmal viele Jahre ehe das vollständige Bild der multiplen Sklerose sich kund tut, gewisse specielle praemonitorische Symptome auftreten, die den Beginn der Krankheit anzeigen. Daher war es für diese Untersuchung von grösster Bedeutung, genaue Rechenschaft über die verschiedenen Aufenthaltsorte der Patienten von ihrer Geburt bis zum Zeitpunkt des Erkrankens und der Aufnahme im Krankenhaus zu erhalten.

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## 2. Die Behandlung des Materials.

### a.) Diagnostische Analyse des zu behandelnden Materials.

Nach Durchsicht des Materials verblieben 1365 Fälle, die Symptomkomplexe aufwiesen, die sich bei der multiplen Sklerose finden. *Richtungsgebend bei der Beurteilung dieser Fälle war das gleichzeitige Vorkommen mehrere Symptome, die auf verschiedene multiple Herde des Nervensystems zurückgeführt werden konnten.*

Pathologisch-anatomische Untersuchung der Fälle war in grösserem Ausmass nicht erfolgt, obwohl das Material hohe Mortalität aufwies. Allerdings dürfte dies darauf zurückzuführen sein, dass die Patienten verhältnismässig selten im Krankenhaus verstorben sind. Gewöhnlich waren die Patienten nur zur Stellung der Diagnose ins Krankenhaus gekommen und dann wieder nach Hause oder in Pflegeanstalten verbracht worden, wo sie später verstarben. Nur in 33 Fällen wurde eine Obduktion vorgenommen und die Diagnose verifiziert. Die pathologisch verifizierten Diagnosen sind also zu gering um von irgend einer Bedeutung bei der Beurteilung des infrage kommenden Materials zu sein.

Wichtiger für die Diagnose war es, dass die Pastorate in einer recht grossen Anzahl von Fällen nach Ableben der Patienten als Todesursache multiple Sklerose angaben. Ein an multipler Sklerose erkrankter Patient stribt gewöhnlich nicht ohne lange schwer krank daniederzulegen zu haben und man darf daher in den meisten dieser Fälle voraussetzen, dass der Arzt, der den Totenschein ausgestellt hat, gute Gelegenheit hatte die Krankheit des Patienten zu studieren.

Nur in einer geringen Anzahl — etwa bei knapp 30 Fällen — bin ich selbst in der Lage gewesen die Patienten zu sehen und zu untersuchen.

Für die Beurteilung des Materials war also so gut wie ausschliesslich das klinische Krankheitsbild und Entwicklung der Krankheit, wie sie die Journale widerspiegeln, entscheidend. Zur Ergänzung dieser Angaben waren die Antworten der versandten Fragebogen von grosser Bedeutung. Hierdurch wurden die zeitigeren Stadien oder intermittierender Verlauf besser aufgehehlt, als dies der Fall gewesen wäre, wenn nur die Angaben der Journale hätten bearbeitet werden können. In einer nicht geringen Anzahl von Fällen wurden hierdurch beispielsweise so wichtige Anfangssymptome wie transitorische Amanrosis, Diplopie oder Paresen verschiedener Art bekannt. So haben viele Fälle, die bei der klinischen Untersuchung nicht besonders symptomreich gewesen, eine Ergänzung der Anamnese erfahren und dadurch an diagnostischer Sicherheit gewonnen. Auch bei der Beurteilung wurde grosses Gewicht sowohl



auf den klinischen Befund bei der Untersuchung wie auf die ergngende Anamnese gelegt.

Infolge der multiplen Herde im Nervensystem entstehen bei der multiplen Sklerose sehr variierende Krankheitsbilder und es ist von verschiedensten Seiten her der Versuch gemacht worden, diese Symptomkomplexe in verschiedene Krankheitsgruppen aufzuteilen. Solche Gruppeneinteilung fand ich neben Anderen bei *Mller*, *Bing-Reese*, *Brain* und *Marburg*. Als erste Gruppe bezeichnen alle die »klassische Form«; ausgezeichnet durch das Vorliegen von *Charcot's Trias*: Nystagmus, skandierendes Sprechen, Intentionstremor und ausserdem oft spastisch-ataktische Symptome, sowie Augensymptome. Die Frequenz dieser Gruppe wird von *Mller* mit 15 %, von *Bing* mit 21 %, von *Brain* mit 10—12 %, von *Marburg* mit 10 %, von *Veraguth* und *Guillain* mit 12 % und schliesslich von *Dibbern* und *Ropers* mit 7 % angegeben. Abgesehen hiervon unterscheiden sich die verschiedenen Gruppeneinteilungen in vielfacher Hinsicht. *Mller* unterscheidet ausser der klassischen Form 4 weitere Gruppen: berwiegend cerebrale Symptome, berwiegend bulbre Symptome, berwiegend spinale Symptome und schliesslich gleichmssiges Vorkommen der cerebralen und spinalen Symptome.

*Bing*, *Brain* und *Marburg* unterscheiden als zweite Gruppe eine symptomreiche cerebrospinale Form, entsprechend *Guillain's forme commune*. Im Grossen gesehen stimmt diese Form mit der klassischen berein und unterscheidet sich von ihr nur dadurch, dass nicht alle Symptome der *Charcot'schen Trias* zu gleicher Zeit vorhanden sind. Es ist die hufigste Gruppe in allen Zusammenstellungen. Ihr folgen dann hemiplegische, paraplegische und spinale Formen unter irgendwie verschiedenen Namen und Abgrenzungen. Alle drei Forscher unterscheiden eine cerebellre Form; charakterisiert durch Ataxie und einige der Symptome in *Charcot's Trias*. *Brain* und *Marburg* unterscheiden weiter eine vestibulre, eine ponticulre und eine bulbre Form mit hauptschlich in den entsprechenden Bezirken lokalisierten Symptomen und schliesslich eine der *Guillain'schen forme  dbut oculaire* entsprechende ophthalmische Form.

Selbstverstndlich ist die Abgrenzung in verschiedene Gruppen recht schwer durchzufhren und in vielen Fllen auch nicht

anwendbar. Meistens werden die Fälle überwiegend einer bestimmten Form entsprechen aber zugleich auch mehr oder weniger in eine oder mehrere der anderen Gruppen hinübergreifen. Die Gruppe, die sich dagegen am leichtesten abgrenzen lässt, ist die klassische, denn sie wird ja durch die *Charcot'sche Trias* bestimmt.

Ich würde hier nicht versucht haben, eine Gruppeneinteilung der Fälle innerhalb meines Materials vorzunehmen, wenn es sich nicht als notwendig erwiesen hätte, um deren Natur aufzuhellen und dadurch herauszubekommen, auf welche Weise in den verschiedenen Fällen die Diagnose gestellt wurde. In einer Arbeit dieser Art ist ja das Material die Grundlage der Untersuchung und ich hätte, wenn dies möglich gewesen wäre, gerne eine ausführliche Journalkausnistik aller Fälle gegeben. Leider wäre dies so kostspielig geworden, dass es für mich ökonomisch nicht durchführbar war. Aber auch wenn es sich darum handelt, die Fälle geographisch zu lokalisieren, ist es von Bedeutung zumindest die klassische Form herauszuheben, dann bei der Kritik meines Materials der verschiedenen Krankenhäuser wurde früher einmal behauptet, dass gewissen Anstalten nur diese, allerdings charakteristischste Form der multiplen Sklerose im wesentlichen bekannt war, dagegen weniger die anderen Formen. Das Material der verschiedenen Krankenhäuser würde deswegen also nicht gleichwertig und auch nicht homogen sein.

Aus diesen Gründen habe ich es für zweckmässig gehalten zu versuchen, die Fälle in gewisse Gruppen einzuteilen und jede Gruppe für sich zu beschreiben. Die dementsprechend von mir aufgestellten Gruppen bilden eine Zusammenfassung der oben citierten Gruppeneinteilungen:

I. Gruppe: Klassische Form, die durch *Charcot's* Trias charakterisiert wird: Nystagmus, Intentionstremor und skandierendes Sprechen ausserdem spastisch-ataktische Symptome und in gewissem Ausmass auch Angensymptome verschiedener Art.

II. Gruppe: Symptomreiche Form, die der ersten Gruppe im Wesentlichen gleicht, nur findet sich bei ihr Nystagmus, Intentionstremor und skandierendes Sprechen nicht gleichzeitig. In diese Gruppe habe ich auch die hemiplegischen und spinalen Formen einbezogen.

III. Gruppe: Cerebelläre Form; die hauptsächlich durch Ataxie und eines oder einige der Symptome der Trias charakterisiert wird.

IV. Gruppe: Bulbäre, vestibuläre und ponticuläre Form, bei der die hauptsächlichsten Symptome denen entsprechen, die bei Schäden in den genannten Bezirken des Nervensystems entstehen.

Die beiden letzt genannten Gruppen greifen in gewissem Sinne ineinander, weshalb die Einteilung hier nur eine ungefähre sein dürfte.

Zur Veranschaulichung will ich einige Typenfälle beschreiben:

Für Gruppe I:

1. Anna W. geb. 1898 (Nr. 1093 des Materials). Behandelt 1926 in Umeå, 1927 in Mörby und 1933 in Skellefteå.  
Erkrankte 1922 an Beinschwäche. 1926 schwankender Gang und Zwangslachen. Status: WR neg. Skandieren, Nystagnus, Intentionstremor, Diplopie, Temporales Erbleichen, Babinski positiv bilateral, Bauchreflexe negativ, Klonus in den Beinen, Romberg positiv, Liquor: N+ P+ Cl. Mors 1939 an Pneumonia.  
Wohnte so gut wie immer in Yttre Ursvik, Skellefteå. Vater Vollbauer.
2. Arvid K. geb. 1899, Briefträger (Nr. 648 des Materials). Behandelt 1928 in Jönköping, 1930 in Lund und 1932 in Värnamo und Jönköping.  
Erkrankte an vorübergehender Facialisparesie 1927 ausserdem Nebel-sehn.  
1928 zittrig in Händen und Beinen, taumelnder Gang. Status: WR neg. Skandieren, Nystagnus, Intentionstremor, Babinski positiv bilateral, Bauchreflexe negativ, Facialisparesie, Romberg positiv. Mors 1934.  
Ständig in Nydala sn. gewohnt. Vater Kossät.

Für Gruppe II:

3. Anna N. geb. 1909, Bauerntochter (Nr. 786 des Materials). Behandelt 1928 in Lund. Erkrankte 1927 an Beinschwäche, Schütteln, Diplopie und Schwindel. Status: WR neg. Nystagnus, Intentionstremor, Temporales Erbleichen, Babinski positiv bilateral, negative Bauchreflexe, schwankenden Gang. Mors 1935.  
Ständig in Vinslöv gewohnt. Vater Landmann.
4. Alma J. geb. 1899, Bauerntochter (Nr. 560 des Materials). Behandelt 1933 in Kristianstad. Erkrankte 1932 an Schwindel, Diplopie, Zwangs-

lachen. Hinzu trat später unsicherer Gang. Status: WR neg. Skandierung, Nystagmus, Temporale Erbleichen, positiver bilateraler Babinski, negative Bauchreflexe, spastischer Gang. Romberg schwankend, Liquor: N+, P+, C4.

Ständig in Skånes Fagerhult gewohnt. Vater Landmann.

#### Für Gruppe III:

5. Daniel L. geb. 1902, Landmann (Nr. 673 des Materials). Behandelt 1929 in Norrköping. Erkrankte 1929 an unsicherem Gang und Schwindel. Status: WR neg. Skandierung, Nystagmus, Romberg positiv, breit-spurriger Gang.

6. Hildur Ö. geb. 1895 (Nr. 1901 des Materials). Behandelt 1931 in Umeå. Erkrankte 1926 an vorübergehender Schwäche des rechten Arms. 1931 Schwäche und Empfindungslosigkeit im rechten Fuss ausserdem Balanzstörung. Status: WR neg. Nystagmus, Romberg positiv, Babinski unsicher, negative Bauchreflexe.

Ständig in Burträsk gewohnt. Vater Landwirt.

#### Für Gruppe IV:

7. Maria K. geb. 1901, Bauerntochter (Nr. 624 des Materials). Behandelt 1927 in Göteborg. 1929 in Alingsås. Erkrankte 1924 an vorübergehender Diplopie und Facialisparesie. 1927 erneut Diplopie. Damaliger Status: Diplopie, Nystagmus und spastische Beinreflexe. 1929 erneut Facialisparesie. Zum Status kam hinzu: Tremor, negative Bauchreflexe und positiver Romberg. Mors 1931.

Ständig in Farsled sn. gewohnt. Vater Landwirt.

8. Hanna W. geb. 1907, Bauerntochter (Nr. 1113 des Materials). Behandelt 1934 in Östersund. Erkrankte 1934 an Sprachverlust und Schwäche in Armen und Beinen. Status: WR neg. hallende Sprache, Temporales Erbleichen, Ptosis, Facialisparesie, Gaumenparesie, negativen Bauchreflex auf der rechten Seite, negativer Babinski. Mors 1934.

Todesursache: multiple Sklerose.

Ständig in Ragunda sn. gewohnt. Vater Arbeiter.

In Tabelle 3 habe ich die verschiedenen Gruppen zusammengestellt, sowie die Frequenz der verschiedenen Symptome für jede Gruppe.

Tabelle 3. Aufteilung des Materials auf 4 Symptomgruppen, Angabe des Vorkommens verschiedener Symptome innerhalb jeder Gruppe und zwar im Prozentverhältnis zur Gesamtzahl aller Fälle der Gruppe.

	Gruppen				
	I	II	III	IV	I-IV
Anzahl der Fälle per Gruppe	68	1051	82	164	1365
Symptome					
Nystagmus	100	51	69	84	59
Intentionstremor	100	15	19	6	18
Skandierendes Sprechen	100	12	19	12	16
Neuritis opt.	38	52	34	59	51
Diplopie	24	19	4	74	25
Facialisparese	8	10	5	26	12
Zungendeviation	2	3	4	12	3
Gaumenparese	2	2	0	5	2
Gehörstörungen	0	1	3	1	1
Parese	16	56	0	0	52
Babinski pos.	73	100	23	20	85
Bauchreflexe neg.	77	67	59	40	63
Sphinkterstörungen	5	12	1	0	9
Klonus	33	32	14	14	29
Romberg	68	59	100	48	60
Gangstörungen	56	49	78	11	46
Ataxie	6	4	60	0	7
Gruppen in % des Gesamtmaterials	5	77	6	12	100

Ans dieser Tabelle erhellt, dass die klassische Form nur 5 % meines Materials ansmacht, eine bedeutend niedrigere Ziffer als die von früheren Verfassern angegebenen. Die gewöhnlichste Form bildet die Symptomreihe mit 77 % diagnosticierten Fällen. Irgendwelche Vergleichsziffer hierfür kann nicht gegeben werden, weil meine Gruppen keinen solchen in früheren Gruppeneinteilungen entsprechen.

In der letzten Kolonne der Tabelle 3 habe ich die relative Frequenz der verschiedenen Symptome innerhalb des gesamten Materials zusammengestellt. Bei Vergleichen der so gefundenen Ziffern mit denen anderer Verfasser ergibt sich eine relativ

gute Übereinstimmung. Angaben der Symptommfrequenz sind von *Müller* aufgestellt worden und in *Brain's* Arbeit findet sich eine tabellarische Zusammenstellung ähnlicher Ziffern von *Birley* und *Dudgeon*, *Sachs* und *Friedmann*, *Marquezy* und *Böhming*. Nur zwei Gruppen von Symptomen kommen bei mir in geringerem Ausmass als von den anderen Forschern angegeben vor und zwar der Intentionstremor und die Sphinkterstörungen. Was den Intentionstremor angeht, so habe ich den Eindruck, dass dies Symptome nicht immer in den Journalen beachtet worden ist. In einem Teil der Fälle nämlich, die ich persönlich untersuchte, traf ich auf deutlichen Intentionstremor, ohne dass irgendwelche Angaben darüber in den Journalen gefunden werden konnten. Im Grossen gesehen scheint, was den Aufbau der Krankheit angeht, zwischen meinem Material und demjenigen der vorher angegebenen Forscher kein Unterschied zu bestehen, was in gewissem Ausmass die Richtigkeit der Diagnosen meines Materials stützen kann.

Tabelle 4.

Monosymptomatischer Krankheitsbeginn mit						
Symptom	Diplopie	Schstörungen	Paresen	Gehstörungen	Schwindelanfälle, Balanzerstörungen	Facialisparese
Transitorische	115	126	247	24	31	8
Zurückgebliebene	17	9	156	68	29	0
Recidiv	62	35	112	2	10	1
Hauptsächlichste S. im zweiten Stadium						
Diplopie	62	18	39	7	4	3
Schstörungen	14	35	27	8	3	3
Paresen	23	40	112	5	2	1
Gehstörungen	6	13	13	2	2	0
Balanzerstörungen	0	3	0	0	10	0
Facialisparese	1	0	8	0	0	1
Sprachstörungen	1	2	2	1	1	0
Sphinkterstörungen	0	0	5	1	1	0
Nicht specificierte Störung	9	15	32	0	9	0

Tabelle 5.

	Polysymptomatischer Krankheitsbeginn				
	Hauptsymptom = S.				
	Diplopie	Sehstörungen	Paresen	Gehstörungen	Schwindelanfälle, Balanzstörungen
Anzahl der Fälle	131	60	115	4	31
S kombiniert mit					
Diplopie	—	2	7	0	2
Sehstörungen	33	—	11	0	0
Paresen	52	20	—	0	2
Schwindelanfälle, Balanzstörungen	51	19	37	0	—
Facialisparese	4	2	1	0	0
Nystagmus	1	1	0	0	0
Gehstörungen	43	23	45	—	21
Sprachstörungen	10	4	16	2	4
Intentionstremor	8	9	7	2	2
Sphinkterstörungen	5	2	19	0	0

Bei der multiplen Sklerose ist zur Beurteilung der Diagnose der Beginn des Erkrankens von entscheidender Bedeutung. Gehört es doch zu ihren charakteristischen Eigenschaften, dass sie oft mit vereinzelt nicht selten vorübergehenden Symptomen beginnt, die viele Jahre bevor die übrigen Symptome der Krankheit sich einfinden auftreten. Mit grösster Sorgfalt habe ich versucht den Beginn der Erkrankung bei den verschiedenen Fällen zu ermitteln und glaube, dass es mir in der grossen Mehrzahl gelungen ist. Hierauf gestützt habe ich eine Einteilung in monosymptomatischen und polysymptomatischen Krankheitsbeginn vorgenommen. In den Tabellen 4 und 5 sind die verschiedenen praemonitorischen Symptome und deren Frequenz zusammengestellt.

In 830 Fällen war der Krankheitsbeginn monosymptomatisch in 347 Fällen polysymptomatisch. Die Zahl der Anamnesen, bei denen der Beginn der Krankheit beurteilt werden konnte, beläuft sich also auf 1177. Bei 556 dieser Fälle waren die ersten Symptome vorübergehend also transitorisch. Diese Fälle ge-

hörten zur monosymptomatischen Gruppe. Von der polysymptomatischen Gruppe waren nur bei 31 Fällen die Symptome vorübergehender Art. Zusammen belaufen sich die Fälle mit vorübergehenden praemonitorischen Symptomen in der Anamnese auf 587, was recht exakt 50 % der studierten Fälle entspricht.

*ZUSAMMENFASSUNG: Das Material, von dem angenommen wird, dass die Diagnose der multiplen Sklerose mit einer gewissen Sicherheit gestellt werden konnte, umfasst 1365 Fälle. Die Diagnose wurde auf Grund von Symptomen gestellt, die auf multiple Herde im Nervensystem zurückgeführt werden können, und in engem Zusammenhang mit einer sorgfältigen Anamnese. Tabellarische Angaben über die Zusammensetzung des Materials werden vorgelegt und zwar sowohl was die ausgebildete multiple Sklerose angeht, wie auch hinsichtlich der praemonitorischen Symptome.*

#### *b) Das auszuschheidende Material.*

735 Fälle wurden auf Grund fehlerhafter oder unsicherer Diagnose ausgeschieden. Da es sich hierbei um einen recht grossen Teil des Materials handelt, will ich diese Fälle hier etwas eingehender behandeln. Es ist natürlich, dass bei einer Krankheit, wie der multiplen Sklerose die unsicheren Fälle häufig sind. Die Jahresberichte an die Königl. Medizinalverwaltung machen zwischen den sicheren und unsicheren Fällen keinen Unterschied. Ein grosser Teil der angemeldeten Fällen mussten somit bei einer Untersuchung, wie der vorliegenden, ausgeschieden werden.

Tabelle 6. Anzahl der unsicheren nicht berücksichtigten Fälle auf die Jahre der Untersuchungsperiode 1925—1934 im Verhältnis zum gesamten Material während derselben Zeit verteilt.

Jahre	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934
Totale Anzahl Fälle	221	245	330	357	345	404	409	418	431	481
Unsichere Fälle	51	74	89	81	71	83	97	93	109	129
Prozentverhältnis	23	29	26	22	20	20	23	22	24	26



Wie aus der Tabelle 6 ersichtlich, verteilen sich die unsicheren Fälle in ungefähr gleichem Verhältnis auf die ganze Untersuchungsperiode. Der Mittelwert liegt bei 24. % der totalen Anzahl und die erhaltenen Ziffern des Prozenzhältnisses weichen von diesem Wert nur unbedeutend ab. Danach kann die Steigerung der Fälle von multipler Sklerose, die aus den Jahresberichten der Medizinalverwaltung ersichtlich ist, nicht darauf zurückgeführt werden, dass nammehr eine grössere Anzahl Fälle mitgeteilt wurden, die früher als unsicher gegolten hätten; denn dann müsste man in der Tabelle ein Steigen der Prozentziffer der unsicheren Fälle im Lanfe der Jahre feststellen können. Das ist aber nicht der Fall, vielmehr liegt die Anzahl der unsicheren Fälle proportional gleich innerhalb aller Jahresgruppen. Dies Verhältnis scheint mir mehr dafür zu sprechen, das die Diagnosestellung mit einer gewissen Einheitlichkeit erfolgte, was ja auch das Wahrscheinlichere, denn man kann erwarten, dass in einer verhältnismässig so kurzen Zeit irgend eine nennenswerte Verfeinerung der Diagnosestellung zu Stande kommt.

Die 735 unsicheren Fälle entsprechen in den Berichten an die Königl. Medizinalverwaltung einer Zahl von 877. Die Verringerung der Fälle hat ihre Ursache darin, dass eine bestimmte Anzahl von Patienten mehrmals verschiedene Jahre im gleichen Krankenhaus behandelt wurden, oder darin, dass der gleiche Fall in mehreren Krankenhäusern eingelegen hat. Allerdings ist die überwiegende Mehrzahl der unsicheren Fälle nicht mehr als einmal im Krankenhaus behandelt worden. In Ziffern ausgedrückt, lagen 616 Patienten einmal im Krankenhaus, was 83 % aller Fälle entspricht; 72 Fälle wurden 2 Mal behandelt, 12 3 Mal, 2 5 Mal, 1 Fall 9 Mal und zwar alle stets im gleichen Krankenhaus. 27 Fällen wurden in verschiedenen Krankenhäusern behandelt und zwar jeweils in zwei Krankenhäusern, ein Fall in drei Krankenhäusern und ein Fall in nicht weniger als vier verschiedenen Krankenhäusern. Zusammengerechnet erhält man für die verschiedenen Fälle 877 geführte Journale, aber nur 735 Patienten, d. h. also, dass bei 13 % die Patienten mehr als einmal im Journal geführt waren. Die entsprechende Ziffer für das gesamte Material beträgt 30 %. Es sei erlaubt, nochmals

darauf hinzuweisen, dass die grosse Mehrzahl dieser unsicheren Fälle nur einmal im Krankenhaus behandelt wurden, denn allein schon dadurch wird die unsichere Natur des Einzelfalles bezeugt.

Bei 26 dieser 735 Fälle waren die Journalangaben über die Krankheit unvollständig oder fehlten gänzlich, so dass die Fälle nicht beurteilt werden konnten.

Bei 9 Fällen sind die Patienten in ein anderes Krankenhaus übersiedelt — gewöhnlich in eines der grösseren Centralkrankenhäuser —, um die zunächst gestellte Diagnose überprüfen zu lassen. In den Journalen dieser Krankenhäuser wurden sie aber in deren Material über multiple Sklerose nicht wiedergefunden, woraus geschlossen werden muss, dass die Diagnose sich später als nicht zutreffend erwiesen hatte. In alle diesen Fällen war übrigens die Diagnose von Anfang an unsicher.

Bei weiteren 9 Fällen erhielt ich auf Grund meines Schriftwechsels mit den Patienten von den Provinzärzten, die diese Patienten in Behandlung gehabt hatten, die Antwort, dass die Diagnose der multiplen Sklerose falsch gewesen wäre.

In 128 Fällen erwies sich die Diagnose später als eine andere oder eine andere war mehr als wahrscheinlich. Die meisten dieser Patienten waren mehrere Male im gleichen Krankenhaus behandelt worden oder hatten in mehr als einem Krankenhause eingelegen. Im nachfolgenden gebe ich eine kurze Analyse dieser Fälle:

In 23 Fällen ergab die Diagnose später Lues cerebrospinalis. Bei 19 dieser Fälle fand sich Lues in der Anamnese und bei 5 derselben war WR positiv im Blut oder Liquor.

In 4 Fällen ergab die Diagnose Tabes dorsalis.

In 16 Fällen lag Tumor cerebri vor und in einem Fall Tumor cerebelli.

In 9 Fällen zeigte es sich, dass die Diagnose Compressionsmyelitis oder Tumor medullae spinalis war.

In 11 Fällen entwickelte sich die Krankheit zur Encephalitis mit Parkinsonismen.

In 2 Fällen war die Diagnose Syringomyelie, in einem progressiv spinale Muskelatrophie, in 2 Fällen spastische Spinalparalyse und in 1 Fall amyotrophische Lateralsklerose.

In 3 Fällen fand man eine Myasthenia gravis.

In 2 Fällen war die Diagnose Meningitis tuberculosa.

In 6 Fällen lag Epilepsie, in einem Schizophrenie und in einem Syndroma Ménière vor.

In 2 Fällen wurden die Symptome von einer Spondylosis deformans verursacht.

In 5 Fällen war die Krankheit sicherlich als Arteriosklerose zu betrachten. Die Patienten waren beim Eintreten der Symptome zwischen 70 und 77 Jahre alt.

In 2 Fällen lag Etylismus chronica vor.

In 6 Fällen muss mit mehr Wahrscheinlichkeit das Vorliegen von Embolien bei Vitium organicum cordis als Diagnose angesehen werden. 3 dieser Patienten hatten zeitiger Embolien gehabt.

In 11 Fällen war die Grundkrankheit Hypertonia arterialis. In einem Fall waren als Symptom Gefühllosigkeit in den Beinen, in 3 Fällen Schwindel, in 7 Fällen Hemiplegien festgestellt.

In 12 Fällen wurden ernstere Grundkrankheiten vorgefunden, davon in 7 Fällen Anaemia perniciosa, in 2 Fällen Diabetes mellitus und in 3 Fällen Thyreotoxikose.

In 1 Fall zeigte sich, dass die Krankheit durch Cancer mit Metastasen im Nervensystem verursacht worden war.

In 4 Fällen entstand die Krankheit unmittelbar im Anschluss an Comotio cerebri, in allen Fällen bei Beginn mit langwährender Bewusstlosigkeit.

In 2 Fällen konnte die Diagnose bei der Obduktion nicht verifiziert werden.

In alle diesen 128 Fällen hat also die spätere Entwicklung der Krankheit gezeigt, dass die vorgeschlagene Diagnose falsch oder unwahrscheinlich gewesen war.

In einer grossen Anzahl von Fällen hatten die Patienten nur eines von Beiden vorgebracht, entweder irgend ein vereinzelter Symptome hauptsächlich etwa Diplopie, Neuritis optica, Spasmodismus im Status. Und zwar sind die hier in Frage kommenden Symptome hauptsächlich etwa Diplopie, Neuritis optica, Spastische Paresen. Die Gruppe umfasst 533 Fälle und ich halte es für begründet, sie hier ziemlich eingehend zu analysieren. Schon die Journaldiagnose dieser Fälle war zumeist mit einem Fragezeichen versehen, ausserdem lagen so gut wie alle Patienten dieser Gruppe nur einmal im Krankenhaus.

In 56 Fällen fand sich in der *Anamnese* Diplopie. In einem dieser Fälle hatten die Patienten auch Schwäche in den Beinen und in 3 Fällen wurde Schwindel und Erbrechen vorgefunden.

*Objektiv* fand man bei diesen Patienten:

In 29 Fällen nur Diplopie, in 6 Fällen ausser Diplopie auch Nystagmus, in 3 Fällen nur Nystagmus, in 2 Fällen Neuritis optica und in einem Fall Neuritis optica und Diplopie. In einem Fall hatte der Patient eine spastische Parese in den Beinen, in einem Fall nur einen positiven Babinski, in einem Fall nur Intentionstremor und Diplopie, in einem Fall unsicherer Gang, in einem Fall Gaumenparese, in 3 Fällen negative Bauchreflexe und in 14 Fällen keine objektiven Symptome.

In 76 Fällen gaben die Patienten in der *Anamnese* Schwindel an. In einem derselben kam zufällig Diplopie vor, in 4 Fällen deutlich Gehstörung und in einem Fall Sprachstörung ausserdem in einem Fall Balanzstörung.

*Objektiv* fand man bei diesen Patienten:

In 27 Fällen Nystagmus, von diesen hatten 6 gleichzeitig positiven Romberg und 1 negative Bauchreflexe, in 13 Fällen wurde positiver Romberg, in 4 Fällen schwankender Romberg, in 6 Fällen Babinski positiv, davon einer mit skandierendem Sprechen, in 2 Fällen lag Diplopie vor und in 2 Fällen unreine Papillen, in 3 Fällen Neuritis optica, in einem Fall unsicherer Gang, in einem Fall Gaumenparese, in 3 Fällen negative Bauchreflexe und in 14 Fällen keine objektiven Symptome.

In 52 Fällen fand sich in der *Anamnese* verringertes Sehvermögen, in einem lag ausserdem Schwindel und Gehstörung vor und in 3 zugleich Schwindel.

*Objektiv* fand man bei diesen Patienten:

44 Fälle von Neuritis optica, 4 Fälle mit unreinen Papillen, 13 Fälle mit zentralen Skotomen, 2 Fälle mit statischen Papillen, der eine mit Nystagmus, der andere mit positivem Romberg, 1 Fall mit Diplopie, 2 Fälle mit positivem Romberg, davon einer mit Erbrechen, 1 Fall von Gaumenparese, 1 Fall mit Facialisparese, 1 Fall mit positivem Babinski und 15 Fälle ohne objektiven Befund.

In 134 Fällen gaben die Patienten in der *Anamnese* Lähmungen oder Schwäche in Armen und Beinen an. In einem dieser Fälle fand sich auch Balanzstörung, in 2 Fällen Tremor, in einem Fall Sprachstörung ausserdem in einem Fall Schwindel.

*Objektiv* fand man bei diesen Patienten:

In 50 Fällen spastische Parese in einem oder beiden Beinen, davon in 2 Fällen auch unsicheren Romberg, in 30 Fällen war Babinski positiv ohne übrige spastische Symptome, in 3 Fällen war Babinski positiv und die Bauchreflexe negativ, in 5 Fällen war Romberg positiv, in einem Fall lag Blasenparese vor, in 8 Fällen Parese in den Beinen mit Fehlen der Reflexe, in 5 Fällen negative Bauchreflexe, davon in einem ausserdem Intentionstremor, in 5 Fällen unsicherer Gang, in einem Fall Diplo-

pie, in 8 Fällen Nystagmus, in 2 Fällen unreine Papillen und in 16 Fällen keine objektiven Symptome.

In 52 Fällen wurden in der *Anamnese* Empfindungslosigkeit in Armen oder Beinen vorgefunden. 2 derselben hatten auch Erbrechen und 2 Paraesthesien in den Beinen.

*Objektiv* fand man bei diesen Patienten:

In drei Fällen spastische Beinparese, in 12 Fällen positiven Babinski ohne andere Symptome, in 2 Fällen positiven Babinski und Nystagmus, in 7 Fällen positiven Romberg, davon in 3 Fällen mit Nystagmus, in 6 Fällen Nystagmus, in 1 Fall Neuritis optica, in 1 Fall Diplopie, in einem Fall stasische Papillen, in einem Fall unsicheren Gang und in zwei Fällen negative Bauchreflexe, in 16 Fällen keine objektiven Symptome.

In 7 Fällen gaben die Patienten in der *Anamnese* Facialisparesie an.

*Objektiv* fand man in allen Fällen Facialisparesie und in 3 Fällen ausser dem Nystagmus.

In 4 Fällen wurde in der *Anamnese* Sprechstörung angegeben.

*Objektiv* fand sich bei diesen Patienten:

In einem Fall skandierendes Sprechen, in drei Fällen unreines Sprechen, davon war ausserdem in 2 Fällen Babinski positiv auf einem Bein und in einem fand sich auch Nystagmus.

In 4 Fällen fand sich in der *Anamnese* plötzlich einsetzende Bewusstlosigkeit.

*Objektiv* fand man bei diesen Patienten:

In 3 Fällen Hemiplegia spastica und in einem Fall Facialisparesie. Alle diese Patienten waren älter.

In 29 Fällen lag Gehstörung in der *Anamnese* vor. In zweien derselben wurde ausserdem Schwindel und Erbrechen vorgefunden. In einem Balancestörung und in einem Taubheit in den Beinen.

*Objektiv* fand man bei diesen Patienten:

In 2 Fällen negative Patellar- und Achillesreflexe, in 3 Fällen Nystagmus, in 7 Fällen positiven Romberg, davon in einem gleichzeitig negative Bauchreflexe und in einem Intentionstremor, in 5 Fällen spastische Paresie in den Beinen, in einem Fall unsicherer Romberg, in 3 Fällen positiver Babinski, in einem Fall unsicheren Gang, in einem Fall ausgesprochene Rigidität in den Beinen und in 6 Fällen kein objektiver Befund.

In 8 Fällen gaben die Patienten Balancestörung in der *Anamnese* an. In einem dieser Fälle wurde gleichzeitig auch Schwäche in den Beinen vorgefunden.

*Objektiv* fand man bei diesen Patienten:

In einem Fall Nystagmus, in 3 Fällen positiven Romberg, in einem Fall Blasenparese, in einem Fall skandierendes Sprechen und in 2 Fällen keine objektiven Symptome.

In 11 Fällen klagten die Patienten in der *Anamnese* über Kopfschmerzen und Erbrechen.

*Objektiv* fand man bei diesen Patienten:

In 4 Fällen Nystagmus, in einem Fall positiven Romberg und in 6 Fällen keinen objektiven Befund.

In 8 Fällen wurde Tremor in der *Anamnese* vorgefunden.

*Objektiv* fand man bei diesen Patienten:

In 2 Fällen Nystagmus, in 2 Fällen Intentionstremor und in 4 Fällen keinen objektiven Befund.

In 16 Fällen gaben die Patienten in der *Anamnese* Rückenschmerzen an. In einem ausserdem Erbrechen, in einem Schwäche der Beine und in einem Gelschwierigkeiten.

*Objektiv* fand man bei den Patienten:

In einem Fall Nystagmus, in einem Fall Neuritis optica, in 3 Fällen spastische Beinparesen, in einem Fall negative Bauchreflexe und in 3 Fällen Intentionstremor, in 7 Fällen keine objektiven Symptome.

In einem Fall lag in der *Anamnese* Urincontinens vor.

*Objektiv* fand man hier nichts.

In 9 Fällen fand man in der *Anamnese* Parästhesien.

*Objektiv* fand man hier:

In 2 Fällen Nystagmus, in 2 Fällen positiven Babinski, in einem Fall Neuritis optica und in einem Fall negative Bauchreflexe, in 3 Fällen kein objektiver Befund.

In 36 Fällen fand man keine *anamnestischen* Symptome.

*Objektiv* fand man bei diesen Patienten:

In 13 Fällen Neuritis optica, in 2 Fällen Diplopie, in 12 Fällen Nystagmus, in 6 Fällen positiven Babinski, davon in einem mit negativen Bauchreflexen, in einem Fall Zungendeviation und in 2 Fällen negative Bauchreflexe.

Zu dieser Gruppe von 533 Fällen kommen ferner 30 unsichere Fälle, die alle im Serafimerkrankenhaus in Stockholm mit unsicherer Diagnose behandelt worden waren und die ich nicht näher analysiert habe.

Auch an die unsicheren Fälle versandte ich das gleiche Frageformular, wie an die sicheren und erhielt in etwa 50 % Antwort. Genau gerechnet antworteten 369 Patienten, wogegen 366 schwiegen. In den eingesandten Antworten konnten nicht die geringsten Anzeichen für das Vorliegen von multipler Sklerose gefunden werden. Die Korrespondenz mit den unsicheren Fällen war etwa 1938 abgeschlossen, während dieser Zeit waren 70

der Patienten verstorben, was 9,5 % des gesamten Materials der unsicheren Fälle ausmacht. Diese Ziffer dürfte nicht höher liegen als diejenige der normalen Bevölkerung während eines gleichen Zeitraums, insbesondere wenn man mitberücksichtigt, dass so gut wie alle hierher gehörenden Patienten der Altersgruppe über 20 Jahren angehören und eine ziemlich grosse Anzahl über 50 Jahre alt waren. Vergleicht man diese Ziffer von 9,5 % mit der Mortalitätsziffer des gesamten berücksichtigten Materials der multiplen Sklerose — einer Ziffer, die mit 25 % errechnet wurde, d. h. 339 Tote auf 1 394 Fälle — so ergibt sich, dass diese nahezu 3 Mal so hoch ist. Natürlich besteht die Möglichkeit, dass ein Teil der Fälle, die ich hier ausgeschieden habe, sich später zu multipler Sklerose entwickeln konnten. Die Observationszeit insbesondere für die im letzten Teil der Untersuchungsperiode behandelten Patienten ist ja recht kurz gewesen, immerhin hat sie mindestens 4 Jahre betragen. Ich habe es aber nicht als möglich angesehen nur auf Grund einzelner solitärer Symptome in Verbindung mit einer unsicheren Anamnese diese Fälle zu beurteilen und sah mich daher gezwungen, sie auszunutzen.

*ZUSAMMENFASSUNG: In 735 Fällen war die Diagnose der multiplen Sklerose unsicher oder falsch. Ausführliche Analyse dieser Fälle wurde gegeben.*

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### **3. Die Beschaffenheit des Materials.**

#### **a) Häufigkeit (Frequenz).**

In der Litteratur finden sich eine Reihe von Angaben, die dafür zu sprechen scheinen, dass die Frequenz der multiplen Sklerose im Zunehmen sei. *Smith* zeigt dies für die USA. bereits in seiner Arbeit von 1904 auf. Mit einer gewissen Berechtigung hat man diese Angabe allerdings darauf zurückgeführt, dass die Erkrankung früher in den USA. relativ wenig bekannt war. Für die späteren Jahre haben unter Anderen *Ahringsmann*, *Schaltenbrandt* und *Voss* auf eine Erhöhung der Frequenz der multiplen Sklerose hingewiesen. Hiervon abgesehen kann man aber

sagen, dass die Angaben über die Frequenz der Krankheit nicht zahlreich sind.

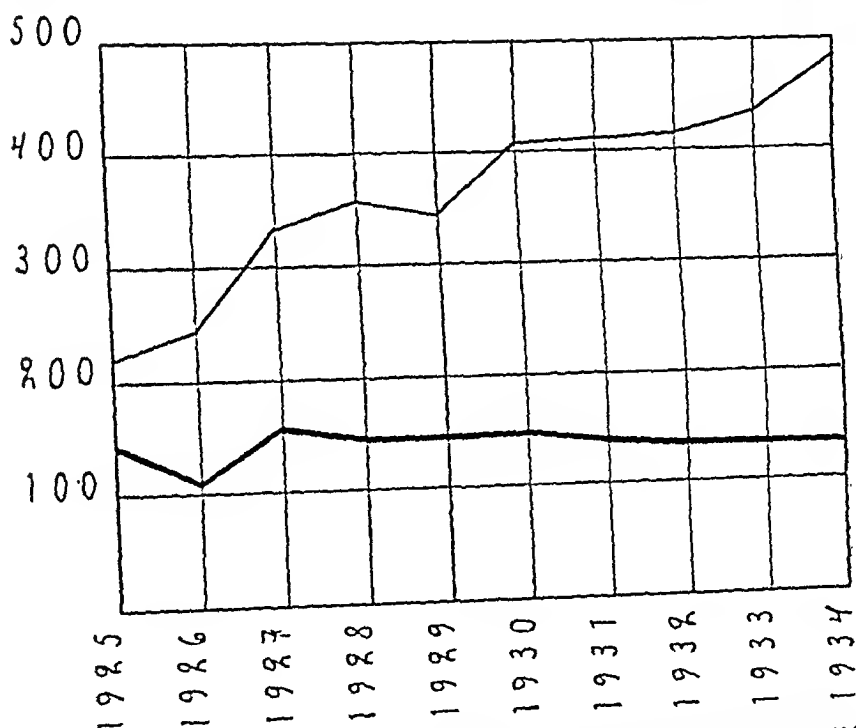
Aus der Tabelle 1 scheint hervorzugehen, dass in Schweden die multiple Sklerose während der Untersuchungsperiode 1925 bis 1934 bedeutend gestiegen ist. Studiert man das Material dagegen eingehender, so kommt man zu einer anderen Auffassung. Wie ich oben bereits darlegte, musste das Material aus bestimmten Gründen höchst bedeutend reduciert werden. Zunächst sind die unsicheren Fälle in ungefähr gleichem Verhältnis in jedem der Untersuchungsjahre weggefallen. Das, was dann hauptsächlich eine Verminderung des Materials zur Folge hatte, war, dass die Patienten nicht einmal, sondern mehrmals im selben Krankenhaus oder mehrfach in verschiedenen Krankenhäusern behandelt worden waren. Auf Grund dessen schrumpfte das Material auf 1365 Fälle von — soweit man dies nach dem Journalmaterial beurteilen kann — sicherer multipler Sklerose.

Tabelle 7 zeigt innerhalb des berücksichtigten Materials die Verteilung der Fälle auf die einzelnen Jahre, wobei zu beobachten ist, dass sie sämtlich zu dem Jahre geführt worden sind, in welchem sie zum ersten Male angemeldet wurden. Mit einer gewissen Überraschung muss man feststellen, dass keinerlei Frequenzerhöhung während der zehnjährigen Untersuchungsperiode statt gehabt hat. In der Figur 1 ist sowohl die Frequenz gemäss den Jahresberichten eingezeichnet worden, als auch diejenige des berücksichtigten Materials. Man wird sich fragen, wie es kommt, dass zwischen den angegebenen Fällen und den in meinem Material berücksichtigten Fällen ein so grosser Unterschied besteht. Bei näherer Betrachtung wird man jedoch feststellen, dass dies auf dem Umstand beruht, dass die Patienten mehrfach im selben Krankenhaus oder in anderen Krankenhäusern behandelt wurden. Und es beruht weiter zu seinem Teil darauf, dass die Patienten während der späteren Jahre meines Untersuchungszeitraums in sehr viel stärkerem Ausmass zum Zweck der Kurbehandlung in Krankenhäuser aufgenommen wurden als früher. Die gewöhnlichste Behandlungsform war Röntgen- und Injektionstherapie. In gewissen Krankenhäusern geschah dies sehr regelmässig, weshalb gerade diese mit hohen Ziffern von multipler Sklerose aufwarten.



Tabelle 7. Die Frequenz der multiplen Sklerose während der Jahre 1925—1934, wie sie aus den Jahresberichten an die Kgl. Medizinalverwaltung erhellt und auf Grund des von mir berücksichtigten Materials.

	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934
Gemäss den Berichten an die Kgl. Medizinalverwaltung.	221	245	330	357	345	404	409	418	431	481
Innerhalb des von mir berücksichtigten Materials.	141	105	155	145	141	148	133	129	135	133



Figur 1. Frequenz der multiplen Sklerose während der Jahre 1925—1934  
 ————— gemäss den Jahresberichten an die Kgl. Medizinalverw.  
 ————— innerhalb des berücksichtigten Materials  
 (Abscisse — Jahr, Ordinate — Anzahl der Fälle.)

Es besteht kein Anlass, der die Erwartung rechtfertigen würde, dass die multiple Sklerose in Schweden angewachsen wäre.

Während der Untersuchungsperiode gab es keine Aufsehen erweckenden Neuheiten auf dem Gebiet der multiplen Sklerose. Die Krankheit war während dieser Zeit ungefähr gleich bekannt und die untersuchenden Aerzte hatten ungefähr die gleiche Ausbildung und studierten dieselben Bücher, (was aus der Umfrage erhellt, die an die Provinzaerzte zur Versendung kam).

**ZUSAMMENFASSUNG:** *Die Anzahl der an multipler Sklerose erkrankten Fälle hat während der Jahre 1925—1934 im Mittel 136 betragen. Eine Erhöhung oder Verminderung während dieser Zeit war nicht wahrzunehmen.*

#### b) Altersverteilung bei der multiplen Sklerose.

Den Zeitpunkt zu bestimmen, an dem die multiple Sklerose beginnt, bietet in vielen Fällen grosse Schwierigkeiten und in einer ganzen Anzahl von Fällen ist es sicherlich nicht möglich irgendwelche zuverlässigen Angaben hierüber zu bekommen. Trotzdem sind die Angaben über die Altersverteilung bei der multiplen Sklerose recht übereinstimmend. *Russel Brain* hat das Material von *Berger, Bing und Reese, Smith, Klausner, Marburg, Morawitz, Müller und Wechsler* zusammengestellt und dabei 1003 Fälle von multipler Sklerose erhalten. Die Altersgruppierung dieser Fälle kann aus nachfolgender Tabelle abgelesen werden.

Tabelle 8.

Altersgruppen	10—20	21—30	31—40	41—50	51—60	über 60
In % der Gesamtsumme	12,0	35,5	32,4	13,3	6,1	1,0

Die überwiegende Mehrzahl der Fälle von multipler Sklerose findet sich also in den Jahren von 21—40. *Levy* sagt, dass sie am gewöhnlichsten zwischen 20 und 38 Jahren wäre, und *Allison* fand ebenso wie *Adie* die meisten Fälle zwischen 20 und 35 Jahren. *Drobnes*, der 103 Fälle der multiplen Sklerose beschrieb, erhielt eine dahin abweichende Ziffer, dass bei ihm eine grössere Anzahl Fälle vor dem 20. Lebensjahr liegen. Zum Vergleich gebe ich *Drobnes'* Tabelle hier wieder.

Tabelle 9.

Altersgruppen	10—20	21—30	31—40	41—50
Fälle	22	25	25	4

Das, was wohl am meisten variiert, wenn es sich um die Altersangaben handelt, sind die Ziffern der Kinderjahre und der höheren Mannesjahre. Man ist jetzt zu der Auffassung gelangt, dass eine infantile multiple Sklerose ebensowenig verneint werden kann, wie eine senile. Allerdings ist die Diagnose im Kindersalter natürlich sehr schwer zu stellen und ein ganzer Teil Fälle dieser Art muss deshalb mit einer gewissen Skepsis betrachtet werden. *Smith* berichtet mehrere Fälle unter 10 Jahren, der jüngste war nur 4 Jahre alt. Vereinzelte Fälle unter zehn Jahren sind auch von *Marburg* und *Bing* beschrieben worden. Dagegen sind in den meisten Statistiken keine Fälle unter zehn Jahren aufgenommen. Ausserdem finden sich so gut wie keine Angaben darüber, ob Fälle aus den Kinderjahren durch Obduktion verifiziert worden sind.

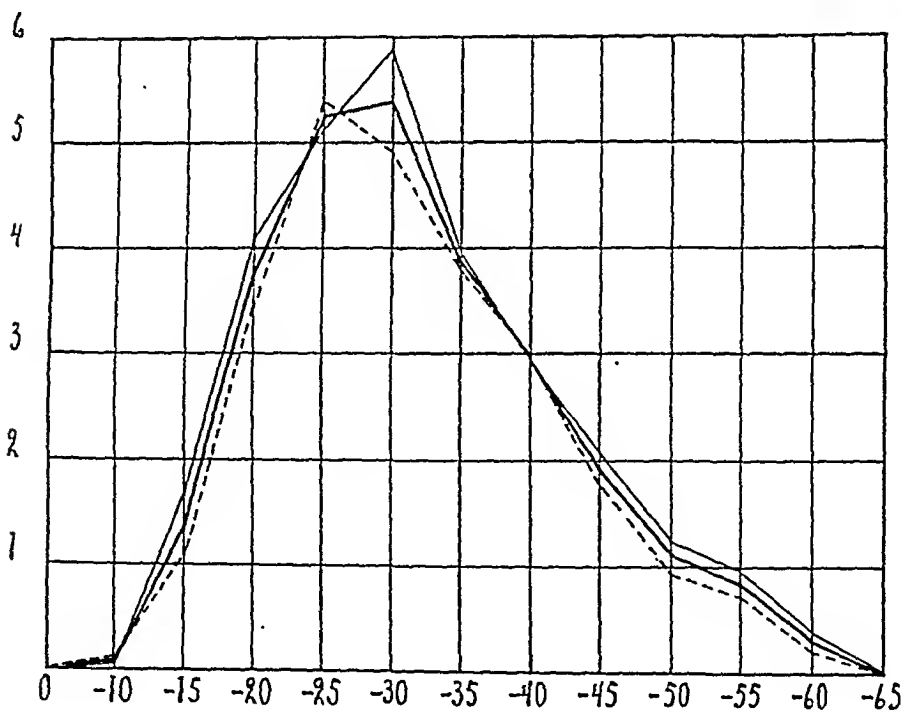
Ebenso schwer ist die Diagnose der multiple Sklerose zu stellen, wenn der Patient bereits ein höheres Alter erreicht hat, denn viele Altersveränderungen können Symptombilder vorweisen, die an diejenigen der multiplen Sklerose erinnern. *Wexberg* und *Marburg* beschreiben trotzdem jeder einen Fall eines weiblichen Patienten, bei dem die ersten Symptome im einen Fall mit 62 im anderen mit 65 Jahren auftraten. In beiden Fällen war die Diagnose durch Obduktion verifiziert. Sonach kann kein Zweifel bestehen, dass es eine senile multiple Sklerose gibt.

Bei 1287 Fällen von 1934 habe ich in meinem Material der multiplen Sklerose versucht das Erkrankungsalter zu bestimmen. Natürlich übergebe ich diese Angaben mit einer gewissen Reservation, denn in einer grossen Mehrzahl von Fällen dürfte es so gut wie unmöglich sein, diesen Zeitpunkt exakt zu bestimmen. Die Angaben sind daher nur ungefährender Natur. Die Fehler müssen bei dieser Untersuchung in einer Verschiebung nach oben gesehen werden, denn in allen zumindest in den meisten Fällen bleibt ein gewisses grösseres oder geringeres Marginal nach unten für die Altersbestimmung beim Erkrankten an multipler Sklerose bestehen.

Die das Erkrankungsalter betreffenden Angaben wurden teils den verschiedenen Krankenhausjournalen entnommen, teils — in mindestens 75, % der Fälle — ergaben sie sich aus der mit den Patienten geführten Korrespondenz. Gerade bei dieser wur-

Tabelle 10.

Altersgruppen	Anzahl der Individuen jeder Altersgruppe $\times 1000$ (a)			Fälle von multipler Sklerose (b)			$\frac{b \times 1000}{a}$		
	Frauen	Männer	Insgesamt	Männer	Frauen	Insgesamt	Frauen	Männer	Insgesamt
5—10	270	280	550	2	3	5	0,07	0,11	0,09
11—15	260	270	530	43	30	73	1,70	1,10	1,38
16—20	278	289	567	112	100	212	4,09	3,50	3,74
21—25	274	276	550	141	148	289	5,15	5,35	5,25
27—30	253	248	501	148	120	268	5,85	4,85	5,34
31—35	232	244	456	91	85	176	3,95	3,79	3,86
36—40	214	199	413	61	58	119	2,86	2,95	2,90
41—45	199	186	385	40	32	72	2,05	1,73	1,87
46—50	177	165	342	22	16	38	1,25	0,97	1,11
51—55	161	152	313	16	11	27	0,99	0,73	0,89
56—60	136	125	261	5	3	8	0,37	0,64	0,31
61—65	120	104	224	0	0	0	0	0	0,00



Figur 2. Die Altersverteilung innerhalb des ganzen Materials von multipler Sklerose (1287 Fälle) in den verschiedenen Altersgruppen.  
 — Frauen    ..... Männer    — Gesamtes Material  
 (Abscisse — Altersgruppen, Ordinate — Relationszahlen.)

de der Zeitpunkt des Erkrankens sorgfältig erfragt. Bei einem Teil der Fälle bin ich dadurch auf der Altersscala ziemlich weit heruntergekommen. Es hat nicht wenig Fälle gegeben, bei denen die sorgfältige Anamnese andere ergeben hat, als sie sich in den entsprechenden Krankenhansjournalen gefunden hatten. Auf diese Weise kamen beispielsweise bei mehreren Fällen vorübergehende Blindheit, Paresen und Diplopien zum Vorschein.

Am Besten lassen sich die näheren Details bei der Altersverteilung an der Tabelle 10 und der Figur 2 studieren.

Man kann aus der Tabelle und aus der Kurve ablesen, dass die multiple Sklerose zweifellos am häufigsten im Alter zwischen 16—35 Jahren auftritt. Summiert man die Anzahl der Fälle innerhalb der Altersgruppen von 16 bis 35 Jahren, so bekommt man 945 Fälle, was berechnet auf die totale Zahl der Fälle, soweit sie hier berücksichtigt wurden, 75 % ergibt. Gewöhnlich findet man in der Litteratur das Alter zwischen 20 und 40 Jahren als dasjenige angegeben, innerhalb dessen die Krankheit am meisten frequent ist. Summiert man in meinem Material diese Altersgruppen, so erhält man 852 Fälle, d. h. 66 % der Gesamtzahl der Fälle.

Irgend einen Unterschied zwischen den verschiedenen Geschlechtern im Hinblick auf das Erkrankungsalter habe ich nicht auffinden können.

*ZUSAMMENFASSUNG: In fast 75 % der Fälle erkranken die Patienten zwischen 16 und 35 Jahren an multipler Sklerose. Nur vereinzelte Individuen erkranken vor dem 10. Lebensjahr. Die Krankheit trifft Frauen und Männer in gleichem Ausmass innerhalb der verschiedenen Altersgruppen.*

c) *Verteilung der multiplen Sklerose auf die einzelnen Geschlechter.*

Die Angaben der Litteratur über die proportionale Verteilung der multiplen Sklerose bei Männern und Frauen weichen recht beachtlich voneinander ab. Bis zu einem gewissen Grad mag dies darauf beruhen, dass in vielen Fällen nur eine kleine Zahl kranker Individuen von den Untersuchungen erfasst wird, was zu fehlerhaften Resultaten führt. Immerhin bleibt beste-

hen, dass sich auch ziemlich bedeutende statistische Arbeiten in diesem Punkte widersprechen. Die Tatsache, dass die Proportionen zwischen Männern und Frauen innerhalb der gleichen Bevölkerung variieren — findet sich doch in den meisten Ländern ein gewisser Frauenüberschuss — kann mitunter diesen Widerspruch erklären. Man hat auch geglaubt, in einzelnen Fällen die Differenzen mit socialen Verhältnissen verschiedener Art zu begründen.

*Smith* fand in seiner Statistik von etwas über 100 Fällen der multiplen Sklerose circa 60 % Männer und 40 % Frauen. Auch *Klausner* hatte vorher ein deutliches Überwiegen der Männer festgestellt. In Übereinstimmung mit diesen Forschern kam ein anderer Teil zu der Auffassung, dass die Krankheit unter Männern gewöhnlicher sei als unter Frauen. So z. Beispiel *Böhmig*, *Russel Brain* und *Kreindler*. *Wechsler* und *Dreyfuss*, die beide aus der zugänglichen Litteratur grosse Zusammenstellungen machten und sich auf solche Weise ein bedeutendes Material verschafften — *Wechsler* 1970 Fälle, *Dreyfuss* 1151 Fälle — fanden übereinstimmend ein deutliches Überwiegen der Männer, wenn es sich um Erkrankten an multipler Sklerose handelte. *Wechsler's* Zifferangabe lautet: 58 % Männer und 42 % Frauen.

Ebenso oft findet man indessen in der Litteratur Angaben darüber, dass die Krankheit in grösserem Umfang das weibliche Geschlecht treffe, eine Ansicht, die *Charcot* schon früher verfochten hat. So gibt *Müller* 1904 an, dass von seinen 75 an multipler Sklerose erkrankten Fällen 40 Frauen und 35 Männer gewesen wären. Die grosse Untersuchung, die *Bing*, *Reese* und *Ackermann* in der Schweiz durchführten, hatte das Ergebnis, dass eine bedeutend grössere Anzahl Frauen an multipler Sklerose leidend befunden wurden als Männer. *Bing* gibt 1931 die Ziffer mit 164 Frauen auf 117 Männern an, und aus späterem Anlass mit 533 Frauen auf 358 Männer. Die Frauen in *Bing's* Material sind also nahezu 33 % zahlreicher als die Männer. Auch wenn man dies zu dem Frauenüberschuss, der in der Schweiz im Mittel auf 8 % geht, in Verhältnis setzt, bleibt für die Frauen hinsichtlich der Erkrankung an multipler Sklerose eine bedeutend höhere Frequenz als für Männer. Zum gleichen

Ergebnis kommen auch *Murburg, Monrad-Krohn, Zellman* und *Adie*.

Ein Teil Forscher findet keinen Unterschied, was das Geschlecht angeht; nach ihrer Auffassung ergreift die Krankheit in gleichem Ausmass Männer, wie Frauen. *Allison* gibt beispielsweise an, dass er bei den 59 Fällen, die er untersuchte, keinen nachweislichen Unterschied zwischen den Geschlechtern fand.

Bei dem von mir untersuchten Material, das aus 1394 Fällen von multipler Sklerose besteht, sind 646 der Patienten Männer und der Rest von 748 Frauen. In Schweden findet sich ein Frauenüberschuss, der 1931 — also zu einem Zeitpunkt, der mitten in die Untersuchungsperiode fällt, die mein Material umfasst — 1029 Frauen auf 1000 Männer betrug. Berücksichtigt man diesen natürlichen Unterschied zwischen den beiden Geschlechtern, so dürfte man an Stelle der gegebenen Zahl nur 665 Frauen auf 646 Männer finden. Nun ist die Anzahl der Frauen in Schweden auf dem Lande proportional geringer als in den Städten. Im Mittel findet man hier 967 Frauen auf 1000 Männer. Bei meinem Material zeigte es sich, dass die Patienten mit multipler Sklerose relativ gleich häufig auf dem Lande wie in den Städten wohnten. 914 wohnten auf dem Lande, der Rest 392 in den Städten. Wenn man den Unterschied der Geschlechterfrequenz in den Städten und auf dem Lande mitberücksichtigt, bekommt man also eher noch eine grössere Differenz der Geschlechter innerhalb meines Materials. Dass der Frauenüberschuss in den Städten 1167 Frauen auf 1000 Männer beträgt, kann das obenstehende Resultat nicht nennenswert beeinflussen, weil ja die Fälle mit multipler Sklerose in den Städten im Verhältnis zu denjenigen auf dem Lande gering sind.

Etwas, das denkbarerweise auf die über das Verhältnis des Vorkommens der multiplen Sklerose unter Männern und Frauen erhaltenen Ziffern einwirken könnte, ist die Tatsache, dass sie am häufigsten, wie ich weiter unten nachweisen werde, zwischen 20 und 40 Jahren auftritt. Studiert man nun wie sich die Volksmenge und ihre Proportionen zwischen Männern und Frauen während dieser Jahre verändern, so kann man feststellen, dass die Anzahl der Frauen nach und nach bedeutend die

Anzahl der Männer übersteigt. Aber auch wenn man dies berücksichtigt kommt man doch nicht annähernd mit einer berechneten Ziffer so hoch, dass sie mit der in dem untersuchten Material erhaltenen verglichen werden kann.

*ZUSAMMENFASSUNG: Die multiple Sklerose kommt häufiger bei Frauen als bei Männern vor; die Differenz ist nicht gross, aber wahrnehmbar. Sie kann mit der wechselnden Zusammensetzung der Bevölkerung in geographisch verschiedenen Bezirken oder in verschiedenen Altersgruppen nicht erklärt werden.*

#### *d) Beruf und Civilstand bei der multiplen Sklerose.*

Eine grosse Anzahl von Arbeiten haben die Frage der Bedeutung des Berufes bei der multiplen Sklerose behandelt. Dabei ist man aus verschiedenen Veranlassungen zu variierenden Resultaten gelangt. Die Untersuchungen sind zumeist auf Grund des Materials einzelner Krankenhäuser vorgenommen und umfassen daher nur die Patienten aus der näheren Umgebung eben dieser Krankenhäuser. Ist beispielsweise der Bezirk um das Krankenhaus herum ein landwirtschaftlicher Distrikt, so überwiegen auch innerhalb des Materials an multipler Sklerose meist Patienten mit zur Landwirtschaft gehörendem Beruf, liegt das Krankenhaus in einem Waldgebiet, so überwiegen Wald- und Holzarbeiter im Material. Wenn daher auf die relative Verteilung der Berufsgruppen innerhalb der Bevölkerung keine Rücksicht genommen wird, so muss man ja in solchen Arbeiten zu ganz verschiedenen Resultaten gelangen.

Zu den ersten, die die Frage des Berufes bei der multiplen Sklerose aufgegriffen haben, gehören *Müller* und *Smith*. In ihren 1904 erschienenen Arbeiten erklären sie übereinstimmend, dass sie dem Beruf der Entstehung der multiplen Sklerose keinerlei Bedeutung beimessen. *Müller* weist noch daraufhin, dass die multiple Sklerose ebenso oft in bemittelten, wie in unbemittelten Kreisen auftritt, wenn man ihr relatives Vorkommen innerhalb dieser verschiedenen Bevölkerungsschichten berücksichtigt.

In den späteren Jahren haben sich unter anderen *Ackermann*, *Allison*, *Bing*, *Brain* und *Marburg* der gleichen Ansicht ange-



schlossen. Auch sie meinen, dass der Beruf für die Entstehung der multiplen Sklerose bedeutungslos sei.

Grosse Verbreitung erfuhr die Ansicht, dass insbesondere Holzarbeiter der multiplen Sklerose besonderes ausgesetzt wären. Unter den grösseren früheren Arbeiten, die diese Ansicht stützen, befindet sich die von *Dreyfuss* 1921 publizierte. *Dreyfuss* fertigte eine Zusammenstellung der an multipler Sklerose erkrankten Patienten, die während der Jahre 1900 bis 1920 in der Litteratur beschrieben worden waren, und fand, dass die Mehrzahl derselben mit Holzarbeiten irgendwelcher Art und mit Landwirtschaft beschäftigt gewesen waren. Auch die Frauen standen auf die eine oder andere Weise gerade mit diesen Berufen in Kontakt. *Russel Bruin*, der '*Dreyfuss*' Arbeit kritisch durchgesehen hat, weist darauf hin, dass man hier die Möglichkeit nicht ausschliessen könne, dass die proportional grosse Verteilung seiner Patienten auf Land- und Holzarbeiter durch ein Übergewicht gerade dieser Berufe innerhalb der Bevölkerung der Gebiete, woher die entsprechenden Fälle stammten, bedingt wäre.

Die nächste grössere Arbeit über die Frage der Bedeutung des Berufes bei der multiplen Sklerose wurde von *Barnass* 1923 vorgelegt. Auch er findet ein Übergewicht der Holzbearbeitenden. Weiter gibt er an, dass das Milieu der Kranken während ihrer Kindheit relativ oft in direkter oder indirekter Verbindung mit den holzbearbeitenden Berufen gestanden habe. *Barnass* stützte seine Bemerkungen auf ein Material von 500 der Versicherungsgesellschaft angemeldeten Militärpersonen, die während ihres Dienstes an multipler Sklerose erkrankten.

Eine ebensolche Untersuchung, wie die von *Barnass* wurde 1929 von *Koch* publiziert. Sie studierte 700 der Versicherungsgesellschaft angemeldete Militärpersonen mit multipler Sklerose. *Koch* sagt, dass von den unterschiedlichen Arten der Handwerkerberufe es sich zeige, dass die Holz- und Metallarbeitenden Berufe in überwiegendem Grad von der multiplen Sklerose erfasst würden, in weniger hohem Masse würden Garten- und Waldarbeiter betroffen. Auch sie meint, dass das Milieu der Kranken in der Jugend relativ oft mit holzbearbeitenden Berufen und mit der Landwirtschaft in Verbindung steht.

*Adams* findet in einer Arbeit 1923 ebenfalls meist Landwirte und Holzarbeiter unter seinen Patienten mit multipler Sklerose und auch in deren Familien überwiegend diese Berufe.

Auch *Böhmig* konstatiert, dass die multiple Sklerose unter den Holzarbeitern zahlreich vorkommt, allerdings treffe sie auch nicht selten Eisen- und Eisenbahnarbeiter.

*McAlpine* glaubt herausgefunden zu haben, dass die Patienten mit multipler Sklerose oft mit praepariertem Holz gearbeitet hätten.

*Steiner*, der das Vorkommen der Krankheit unter Soldaten untersuchte, findet, dass die, die zumeist von multipler Sklerose getroffen werden, Pioniere sind und unter diesen wieder besonders Zimmerleute und Schreiner.

*Wilson* studierte die Mortalitätszahlen der multiplen Sklerose innerhalb gewisser Berufsgruppen und kam zu dem Ergebnis, dass die Ziffern für Landarbeiter mindestens doppelt so hoch, wie die für die anderen Berufe wären, aber auch er fand ein gewisses Übergewicht, was die Mortalitätsziffer betreffe, für Zimmerleute, Maler und Gartenarbeiter.

*Kreindler*, der die Krankheit in Rumänien studierte, kam zu einer etwas abweichenden Auffassung. Er meint, dass die multiple Sklerose meist bei Städtern und dort wieder bei im Handwerkerberuf beschäftigten Personen vorkäme.

Aus der citierten Litteratur geht deutlich hervor, wie schwer, ja beinahe unmöglich es ist, auf Grund kleinen unzufriedenstellend geographisch-pathologisch durchgearbeiteten Materials von multipler Sklerose eine sichere Auffassung über eine nachgerade so elementare Sache wie den Beruf und seine Bedeutung für die Entstehung der Krankheit zu erhalten.

In recht beachtlicher Hinsicht ist das von mir hier vorgelegte Material besser geeignet die aufgeworfene Frage zu studieren als irgend ein vorher zugänglich gemachtes Material der multiplen Sklerose. Zunächst besteht das Material aus gleichmässig im ganzen Land (Schweden) während einer zehnjährigen Periode gesammelten Fällen. Diese Gleichförmigkeit dürfte mit geringen Abweichungen auch bei Beurteilung der verschiedenen Krankheitsfälle in den verschiedenen Teilen des Landes vorhanden gewesen sein. Ausserdem ist Schweden ein in jeder Hin-

sicht gut geordnetes Land mit insbesondres vorzüglich organisierter statistischer Behandlung der demographischen Verhältnisse.

Um eine sichere Grundlage für die Beurteilung der Frage nach der Bedeutung des Berufes bei der multiplen Sklerose zu

Tabelle 11. Spezifizierte Angaben über die Berufsverteilung bei den Patienten mit multipler Sklerose. Die Frequenz (F) = die Anzahl der Fälle pro 10 600 Individuen innerhalb der verschiedenen Berufsgruppen.

Landbau und Viehzucht				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Landarbeiter mit Tieren	95	0	0	0
Landarbeit., nicht spezifiziert	122	0	530	0
Gutseigentümer	0	0	4	0
Gartenarbeiter	3	0	6	0
Meiereiarbeiter	3	2	0	1
Stallknechte	18	0	13	0
Tischler im Landbau mit Tieren	2	0	0	0
Tischler im Landbau ohne Tiere	6	0	10	0
Schmiede im Landbau	2	0	11	0
Dienstvolk im Landbau mit Tieren	0	39	0	0
Dienstvolk in Landbau ohne Tiere	0	12	0	0
Bauerntochter beim Bauern:				
Bauerntochter beim Bauern mit Tieren	0	69	0	0
Bauerntochter beim Bauern ohne Tiere	0	60	0	0
Bauersfrau mit Tieren	0	59	0	(96)
Bauersfrau ohne Tiere	0	37	0	0
Haushaltarbeiter auf dem Hof:				
Haushaltarbeiter auf dem Hof mit Tieren	0	22	0	0
Haushaltarbeiter auf dem Hof ohne Tiere	0	14	0	0
S u m m e	251	314		
	565		574	1(96)
Bevölkerungsmenge innerhalb der Berufsgruppe: 2043 258	F = 2,7		F = 2,8	

Fischerei				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Fischer	2	0	5	1
	2	0		
S u m m e	2		5	1
Bevölkerungsmenge innerhalb der Berufsgruppe: 41 494	F = 0,5		F = 1,2	

Wald- und Forstwirtschaft				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Waldwächter, Jagdmeister	2	0	6	1
Waldarbeiter	29	0	16	3
Flößer	3	0	3	0
Flosschef	0	0	1	0
	31			
S u m m e	31		26	4
Bevölkerungsmenge innerhalb der Berufsgruppe: 182 023	F = 1,5		F = 1,4	

Erzbergbau-, Mineral-, Metall- und Maschinenindustrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Erzgrubenarbeiter	2	0	7	3
Eisenerwerksarbeiter	19	0	13	3
Mechanische Werkstattarb.	19	0	12	3
Schmiede, Schmiedearbeiter	3	0	9	2
Kupferschläger	0	0	1	0
Uhrmacher	0	0	2	0
Goldschmiede	2	0	1	0
Ingenieure	5	0	1	1
S u m m e	50			
	50		40	12
Bevölkerungsmenge innerhalb der Berufsgruppe: 464 776	F = 1,1		F = 0,9	

Industrie der Erden und Steine				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Kohlenträger	0	0	1	0
Steinarbeiter	4	0	16	1
Kalk- und Zementarbeiter	1	0	2	0
Ziegel- und Porzellanarbeiter	2	0	3	2
Glasarbeiter	3	1	4	0
S u m m e	10	1		
	11		26	3
Bevölkerungsmenge innerhalb der Berufsgruppe: 130 327	F = 0,8		F = 2,0	

Holzwarenindustrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Sägewerksarbeiter	13	0	13	0
Holzarbeiter	5	0	2	1
Schreiner	6	0	4	0
Wagenmacher	0	0	1	0
Böttcher- Korbmacher	1	0	2	0
	25	0		
S u m m e	25		22	1
Bevölkerungsmenge innerhalb der Berufsgruppe: 270 135	F = 0,9		F = 0,8	

Papier- und Graphische Industrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Papierarbeiter	8	0	4	0
Buchbinder	0	1	0	0
Buchdrucker	1	0	1	0
Typographen	7	0	3	0
Photographen	0	1	0	0
	16	2		
S u m m e	16		7	0
Bevölkerungsmenge innerhalb Berufsgruppe: 142 343	F = 1,3		F = 0,5	

Nahrungs- und Genußmittelindustrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Mühlennarbeiter, Müller	2	0	11	0
Bäckerei	4	4	2	1
Chokoladenarbeiter	1	0	0	0
Zuckerfabrik	1	0	1	0
Schläckereiarbeiter	7	0	10	1
Konservenarbeiter	0	1	0	0
Brauereiarbeiter	2	0	7	0
S u m m e	17	5		
	22		31	2
Bevölkerungsmenge innerhalb der Berufsgruppe: 147 235	F = 1,5		F = 2,1	

Textil- und Bekleidungsindustrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Spinnerel	0	0	1	0
Weberel	4	3	3	0
Wäscheplätten	0	3	0	0
Stickerin	0	5	0	0
Helmnäherin	4	37	15	2
Fabriknäherin	0	1	0	0
S u m m e	8	49		
	57		19	2
Bevölkerungsmenge innerhalb der Berufsgruppe: 209 106	F = 2,7		F = 0,9	

Leder-, Haar- und Gummiindustrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Gärbereiarbeiter	2	0	4	0
Schuhmacher	6	0	9	3
Schuhfabriksarbeiter	2	5	0	0
Sattler	1	0	3	0
Gummiarbeiter	1	1	0	0
Barbier	0	0	3	0
	12	6		
S u m m e	18		19	3
Bevölkerungsmenge innerhalb der Berufsgruppe: 118 866	F = 1,6		F = 1,6	

Chemisch-technische Industrie				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Oel-, Seife- und Lichtarbeit	0	0	2	0
Galvaniseur	1	0	0	0
Pulverarbeit	3	0	1	0
Streichholz-sulfat-fabriks- arbeiter	2	1	2	0
	6	1		
S u m m e	7		5	0
Bevölkerungsmenge innerhalb der Berufsgruppe: 45 857	F = 1,5		F = 1,1	



Baugewerbe, Beleuchtung, Wasserleitung				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Bauarbeiter	4	0	5	0
Schachtarbeiter	12	0	18	3
Maurer	0	0	6	1
Anstreicher	18	0	8	0
Schreiner	8	0	20	0
Rohrleger	4	0	0	2
Klempner	2	0	2	0
Gasarbeiter	1	0	0	2
Elektriker	9	0	4	2
Strassenreinigung	1	0	1	0
Ingenieure	6	0	5	0
S u m m e	65	0		
	65		69	10
Bevölkerungsmenge innerhalb der Berufsgruppe: 310 822	F = 2,1		F = 2,2	

Handel				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Händler, Geschäftsleute	12	0	29	2
Kontoristen	23	13	3	5
Handelsreisende	7	0	1	2
Verkäufer	11	22	0	0
Lagerarbeiter	3	0	6	2
Hotelarbeiter	2	4	0	0
Kellnerin	0	5	2	0
S u m m e	58	44		
	102		41	11
Bevölkerungsmenge innerhalb der Berufsgruppe: 390 186	F = 2,6		F = 1,0	

Verkehr				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Post	3	3	2	1
Telegraph	1	5	0	0
Eisenbahn	18	0	21	0
Strassenbahn	2	0	0	0
Fuhrunternehmer und Arbeiter	4	0	6	0
Chauffeur	12	0	2	0
Transportarbeiter	2	0	0	1
Seekapitän	0	0	8	0
Seemann	5	0	5	0
Maschinist, Schiffsheizer	8	0	3	2
	55	8		
S u m m e	63		47	7
Bevölkerungsmenge innerhalb der Berufsgruppe: 367 757	F = 1,7		F = 1,3	

Hausarbeit				
	Pat. mit multipler Sklerose		Beruf des Vaters	Beruf des Gatten
	Männer	Frauen		
Hausgehilfin ohne spezifizierte Arbeit	1	70	1	0
Hausmeister	0	0	1	0
	1	70		
S u m m e	71		1	0
Bevölkerungsmenge innerhalb der Berufsgruppe: 219 384	F = 3,2		F = 0,5	

bekommen, habe ich bei meiner Arbeit versucht die verschiedenen Berufsstände der Patienten so genau wie möglich zu spezifizieren. In 1177 der 1384 Fälle konnten sichere Angaben über die Berufungsverhältnisse erlangt werden. Die Verteilung dürfte sich am einfachsten an den Tabellen 11 und 12 studieren lassen. In diesen Tabellen bin ich derselben Gruppeneinteilung gefolgt, wie sie im Schwedischen Statistischen Jahrbuch von 1932 enthalten, und habe aus ihm auch Ziffern über die in verschle-

Öffentlicher Dienst und freie Berufe		Pat. mit multipler Sklerose		Beruf des Vaters		Beruf des Gatten	
		Männer	Frauen				
Summe	Bevölkerungsmenge innerhalb der Berufsgruppe: 271 270	F = 2,6		F = 1,3			
		72		35		11	
		31	38				
Offizier		1	0	3		1	
Mauschulden		4	0	8		2	
Polizist		1	0	3		2	
Feuerwehrmann		0	0	0		1	
Geldhelfer		0	0	0		0	
Organist		0	0	6		0	
Kirchenliedner		1	1	1		0	
Kleinbinder- und Volksschul-		2	0	3		1	
Lehrer		9	18	7		0	
Gewerbelehrer		0	2	0		0	
Lehrer		0	1	1		0	
Arzt		0	1	1		0	
Med. Student		1	1	0		2	
Thierarzt		1	0	0		0	
Apotheker		1	0	0		0	
Hebamme		0	3	0		0	
Krankenschwester		0	4	0		0	
Krankenhelfer/in		0	5	0		0	
Höherer Beamter		1	0	1		2	
Student		9	3	0		0	

denen Berufsgruppen beschäftigte Anzahl von Individuen erhalten. Allerdings begründet sich diese Zifferangaben auf denen des Jahres 1920 also einer etwas früheren Periode als der von mir untersuchten der Jahre 1925—1934. Ich glaube aber nicht, dass sich die Relation zwischen den verschiedenen Berufsgruppen während dieser kurzen Zeitspanne in irgendeinem nennenswerten Grad verändert haben dürfte.

Ich habe in den Tabellen auch den Beruf des Vaters oder Gatten jeweils in einer Kolumne aufgeführt. In 926 Fällen hat sich der Beruf des Vaters bestimmen lassen.

Am Schluss der Tabellen über jede Berufsgruppe ist das relative Vorkommen der zu der betreffenden Berufsgruppe gehörigen Fälle von multipler Sklerose auf 10000 Einwohner ( $F/10000$ ) berechnet worden. Dies geschah sowohl für die Fälle der multiplen Sklerose, wie für die Väter der Patienten mit multipler Sklerose. Tabelle 12 bietet nur eine Zusammenstellung dieser Resultate.

Aus den Tabellen können wir entnehmen, dass die multiple Sklerose am häufigsten bei Personen zu sein scheint, die mit häuslicher Arbeit beschäftigt sind. Dennoch muss diese Berufsgruppe bei meinem Material mit einer gewissen Reservation aufgenommen werden, weil die Patienten, die angegeben haben, mit häuslichen Arbeiten beschäftigt zu sein, mitunter wahrscheinlich zu einer der anderen Berufsgruppen hätten zugezählt werden können, wenn noch genauere Differenzierung möglich gewesen wäre. Besonders die verheirateten Frauen innerhalb dieser Gruppe könnten sicherlich zu einem grossen Teil unter der Berufsgruppe ihrer Männer geführt werden. Die Ziffer  $3,2/10000$  erscheint sonach etwas gross und dürfte in Wirklichkeit geringer sein.

Eine Frequenz von über  $2,5/10000$  finden wir innerhalb der Berufsgruppen Landbau, Textilindustrie, Handel, öffentlicher Dienst und freie Berufe. Die Landbantreibenden liegen also recht hoch auf der Skala, aber nicht annähernd so hoch, wie man sie früher veranschlagte. Indessen scheint ein gewisses, obwohl kleines Übergewicht beim Landbau vorzuliegen, wenn man auch auf den Beruf des Vaters Rücksicht nimmt, der mit  $2,8/10000$  ebenfalls zu dieser Berufsgruppe gehört. Betracht-

tet man die totale Anzahl der Fälle innerhalb dieser Gruppe, so ist man zweifellos von der grossen Zahl für die Patienten mit multipler Sklerose, wie auch derjenigen für den väterlichen Beruf frappiert. Allerdings sind, wie man gleichzeitig feststellen kann, nicht weniger als 2 Millionen Menschen im Lande gerade innerhalb dieses Berufszweiges beschäftigt. Auf diese Weise wird es leicht den Fehlschluss in mehreren der oben citierten Arbeiten zu verstehen, wenn man dieses zweifellose Übergewicht der landbanenden Bevölkerung in Betracht zieht.

Dass die Textilgruppe so hoch kommt beruht auf den recht zahlreichen Heimgewerbetreibenden. Die übrigen Beschäftigten dieser Gruppe sind zahlenmässig unbedeutend.

Beim Handel entfällt der Hauptteil der Fälle auf Kontoristen und Verkäufer — insgesamt 68 Stück, davon 34 Männer und 34 Frauen. Was schliesslich die letzte Gruppe über 2,5/10000 betrifft — öffentlicher Dienst und freie Berufe — so hat es den Anschein, als ob die Mehrzahl der dorthin gehörenden Patienten als Kleinkinder- und Volksschullehrer und -lehrerinnen beschäftigt waren; denn nicht weniger als 27 Patienten, 9 Männer und 18 Frauen gehören in diese Berufssparte. Im übrigen verteilt sich die Krankheit ziemlich gleichmässig auf die anderen Berufe der Gruppe.

Es ist von Interesse, dass die multiple Sklerose gerade innerhalb dieser Gruppe so verhältnismässig häufig vorkommt; denn ein allgemeiner Eindruck geht ja dahin, dass gerade die sogenannten gebildeten Berufe der Krankheit nicht so ausgesetzt wären, wie die mehr körperlich arbeitenden. Meine Ergebnisse widersprechen recht deutlich dieser Behauptung.

Das Vorkommen der multiplen Sklerose innerhalb der übrigen Berufsgruppen variiert in ganz kleinen Grenzen. Dasselbe ist der Fall mit Bezug auf den väterlichen Beruf.

Die Angaben darüber inwieweit die multiple Sklerose häufiger bei verheirateten oder unverheirateten Frauen vorkommt, sind sehr spärlich. Der einzige, der eine grössere Untersuchung hierüber angestellt hat, ist *Wechsler*. Er gelangt zu der Meinung, dass der Civilstand von keiner Bedeutung für die Krankheit sei, findet sie aber gewöhnlicher vorkommend bei verheirateten Frauen. Das sei nach seiner Ansicht erklärlich, weil die

Tabelle 12. Die Verteilung der multiplen Sklerose innerhalb der verschiedenen Berufe.

Berufsgruppen	Bevölkerungsmenge innerhalb der Berufsgruppe	Anzahl der Fälle von mult. Skler.	F/10000	Zahl der innerhalb des Berufs beschäftigten Väter	F/10000
Landbau und Viehzucht	2.043.258	565	$2,7 \pm 0,1$	574	2,8
Fischerei	41.494	2	$0,5 \pm 0,3$	5	1,2
Wald- und Forstwirtschaft	182.023	34	$1,9 \pm 0,3$	26	1,4
Erzbergbau-, Mineral-, Metall- Maschinen-industrie	464.776	50	$1,1 \pm 0,1$	40	0,9
Industrie der Erden und Steine	130.327	11	$0,8 \pm 0,2$	26	2,0
Holzwarenindustrie	270.135	25	$0,9 \pm 0,2$	22	0,8
Papier- und graphische Industrie	144.343	18	$1,3 \pm 0,3$	7	0,5
Nahrungs- und Genussmittelindustrie	147.235	22	$1,5 \pm 0,3$	31	2,1
Textil- und Bekleidungsindustrie	209.106	57	$2,7 \pm 0,3$	19	1,0
Leder-, Haar- und Gummiindustrie	118.866	18	$1,6 \pm 0,3$	19	1,6
Chemisch-technische Industrie	45.857	7	$1,5 \pm 0,4$	5	1,1
Baugewerbe, Beleuchtung, Wasserleitung	310.822	65	$2,1 \pm 0,3$	69	2,2
Handel	390.186	102	$2,6 \pm 0,2$	41	1,0
Verkehr	367.757	63	$1,7 \pm 0,2$	47	1,3
Öffentlicher Dienst und freie Berufe	271.270	72	$2,6 \pm 0,3$	35	1,3
Hausarbeit	219.381	71	$3,2 \pm 0,4$	2	0,5

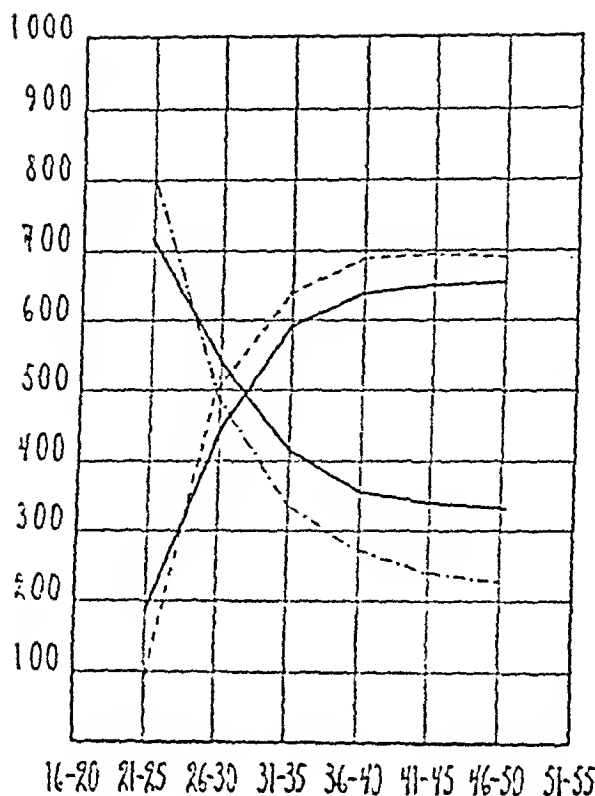
grösste Anzahl Frauen in den Jahren zwischen 20 und 50, während deren die Krankheit am häufigsten wäre, verheiratet seien.

Die Anzahl der Frauen meines Materials beträgt 748. In einem Teil der Fälle war es unmöglich Angaben darüber zu erhalten, ob die Frauen verheiratet oder unverheiratet waren. Rechnet man diese Fälle ab, so bleiben 690 Frauen. Von diesen waren 291 verheiratet und 399 unverheiratet, als sie im Krankenhaus behandelt wurden. Bei einem Teil der Fälle konnte nicht ausgemacht werden, ob die Patientinnen zur Zeit der Erkrankung verheiratet waren oder nicht. Rechnet man auch diese unsicheren Fälle ab, so bleiben 636 Fälle und von diesen waren 268 verheiratet und 368 unverheiratet. Ist diese Proportion nun die normale oder überwiegt ein Teil über den anderen? Zur Beantwortung dieser Frage verweise ich auf die Tabelle 13 und die Figur 3. In der Tabelle habe ich die relativen Zahlen für die verheirateten und die unverheirateten Patientinnen mit multipler Sklerose per 1000 Fälle berechnet. Im Bild findet man diese Relationszahlen (d. h. die Zahl, die bei successivem Ausgleich aus diesen Zahlen errechnet wurde) zusammen mit entsprechenden Zahlen für die gesamte weibliche Bevölkerung der vergleichbaren Altersgruppen eingezeichnet.

Tabelle 13. Verteilung der verheirateten und der unverheirateten Patientinnen mit multipler Sklerose innerhalb der verschiedenen Altersgruppen.

Altersgruppe	Verheiratet	Unverheiratet	Summe	Relative Zahlen pro 1000 Fälle	
				Verheiratete	Unverheiratete
16—20	5	102	112	85	915
21—25	41	100	141	290	710
26—30	72	76	148	486	514
31—35	50	41	91	549	451
36—40	45	16	61	737	263
41—45	25	15	40	625	375
46—50	13	9	22	590	410
51—55	12	4	16	750	250
56—60	5	0	5	1000	0
	268	368	636		

Aus Figur 3 und der Tabelle 13 geht hervor, dass sowohl absolut, wie relativ die verheirateten Frauen geringer als die un-



Figur 3. Das Verhältnis zwischen unverheirateten und verheirateten Frauen pro 1000 Fälle in verschiedenen Altersgruppen von 21 bis 50 Jahren. Die punktierten Kurven zeigen das Verhältnis für die weibliche Bevölkerung des ganzen Landes, — — — verheiratete Frauen, — · — · — unverheiratete Frauen. Die ausgezogenen Linien entsprechen den Kurven für weibliche Sklerosefälle.

verheirateten sind. Weiter kann man wahrnehmen, dass bei den Jahresgruppen von 20 bis 30 Jahren sich die Kurve der gesamten weiblichen Bevölkerung und diejenige der Patienten mit multipler Sklerose beachtlich nähern. Darüber hinaus besagen sie, dass die Kurve der unverheirateten proportional nicht mit der gleichen Schnelligkeit sinkt, wie die entsprechende der gesamten Bevölkerung. Wir erinnern uns, dass alle Patientinnen des hier abgehandelten Materials bereits verheiratet waren, als sie von der Krankheit befallen wurden. Nun trifft die multiple Sklerose zumeist Personen im Alter von 16—35 Jahren. Es kommt vereinzelt vor, dass eine Patientin, nachdem sie an un-



tipler Sklerose erkrankte, sich verheiratet hat, gewöhnlich ist es nicht. Also erscheint es durchaus natürlich, dass wir jenseits des dreissigsten Lebensjahres mehr unverheiratete und weniger verheiratete Patientinnen mit multipler Sklerose beobachten, als bei den entsprechenden Proportionen der gesamten Bevölkerung.

*ZUSAMMENFASSUNG: Eine sorgfältige Studie darüber, wie sich die einzelnen Berufe auf die Patienten der multiplen Sklerose verteilen, zeigt ein unbedeutendes Überwiegen der innerhalb der Landwirtschaft, der Textilindustrie, des Handel, des öffentlichen Dienstes und der freien Berufe beschäftigten Personenkreises. Von Interesse ist es, wahrzunehmen, dass die Zahlen der aus der Landwirtschaft an multipler Sklerose erkrankten Patienten und diejenigen, deren Eltern aus der Landwirtschaft stammen oder in ihr beschäftigt waren sich entsprechen. Ein Überwiegen der in der Landwirtschaft beschäftigten Personen wird hierdurch wahrscheinlicher.*

e) Über die familiären Verhältnisse bei der multiplen Sklerose.

1.) Nerven- und Geisteskrankheiten.

Nach einer verbreiteten Ansicht soll es besonders ungewöhnlich sein, mehrere Fälle von multipler Sklerose in ein und derselben Familie anzutreffen. So meint *Strümpell* 1918, dass man so gut wie niemals die multiple Sklerose bei Geschwistern beobachte. Trotzdem sind die Angaben über ein Vorkommen der multiplen Sklerose in den Familien der Erkrankten in der Literatur keineswegs gering. Zumeist handelt es sich hierbei um Mitteilungen einzelner Fälle, seltener um Studien der Vererblichkeit in grösseren Materialzusammenstellungen. Wenn ich daher nunmehr Litteratur zu dieser Frage citiere, so erhebe ich keinen Anspruch darauf, hiermit alles erfasst zu haben, was auf diesem Gebiet geschrieben wurde, meine Absicht ist vielmehr lediglich einige Beispiele aus einschlägigen Schriftum zu geben. So werden beispielsweise einzelne Fälle von *Curschmann* zunächst 1920 und später 1938 berichtet. Er stellte multiple Sklerose bei der Schwester des Vaters und dem Neffen, und bei 3 Brüdern fest. Für diese letzteren ist es von Interesse darauf hin-

znweisen, dass alle Brüder zu verschiedenen Zeitpunkten erkrankten und dass sie alle verschiedene Symptome aufwiesen.

*Simon* beschreibt zwei Familienfälle, den einen bei Mutter und Tochter, den anderen bei zwei Brüdern.

Das Vorkommen der multiplen Sklerose bei eineiigen Zwillingen ist unter anderem von *Jentsch* beschrieben. Auch hier ist es von Interesse, dass die beiden Zwillinge nicht gleichzeitig erkrankten, sondern mit einem Zwischenraum von 12 Jahren. Einen ähnlichen Fall von eineiigen Zwillingen beschreibt *Curtius*. Hier erkrankte der eine Zwilling mit 24 Jahren und der andere mit 48 Jahren.

*Bing* sagt, dass er in seinem grossen Material aus der ganzen Schweiz (891 Fälle von multipler Sklerose) in 13 Fällen belastete Familien gefunden hätte, hiervon 6 mal bei Geschwistern, 2 mal bei Vater und Tochter, einmal bei Mutter und Sohn, einmal bei Mutter, Son und Tochter, ausserdem 2 mal bei Vettern. Wenn man die Proportionen dieser Familienbelastung mit multipler Sklerose in *Bing's* Material berechnet, erhält man als Ziffer 1,44 %.

*Allison* fand in seinem Material von multipler Sklerose (65 Fälle) in 2 Fällen multiple Sklerose in der Familie. Bei beiden Fällen handelte es sich um Geschwister.

*Marburg* beschreibt 3 Fälle von multipler Sklerose in Familien bei einem Material von 152 Patienten und kommt zu dem Schluss, dass ohne Zweifel eine direkte Heredität bei der multiplen Sklerose existiert.

*Steiner* beschreibt multiple Sklerose bei 2 Schwestern.

Eine sorgfältige Untersuchung auf diesem Gebiet ist von *Curtius* publiziert worden. Er untersuchte die Familienverhältnisse in 106 Fällen von multipler Sklerose genau und fand unter 212 untersuchten Eltern nur 1 Fall von unsicherer multipler Sklerose, dagegen unter 444 Geschwistern 4 sichere und einen unsicheren Fall. Er berechnet das prozentuale Vorkommen in der Familie mit 1,35 % und vergleicht es mit dem von *Bing* erhaltenen. Das Vorkommen der multiplen Sklerose in der gesamten Schweiz wird mit 0,023 % berechnet. Für *Curtius* bildet die bedeutende Steigerung der Krankheitsfrequenz unter Geschwistern und nahen Verwandten den Beweis dafür, dass erb-

Tabelle 14. Die familiäre Belastung mit Nerven- und Geisteskrankheiten innerhalb des untersuchten Materials (1010 Fälle).

	1. Generation		2. Generation			Generation des Patienten		Eligene Kinder des Pat.	In der Verwandtschaft	Summe
	Grosseltern		Vater	Mutter	Deren Geschwister	Geschwister	Vetter und Cousins			
	männlich	weiblich								
Multiple Sklerose	0	0	1	1	0	15	0	0	2	19
Ähnliche Krankheiten	0	2	4	7	7	15	7	0	1	43
Epilepsie	1	0	2	0	5	5	0	1	2	16
Migräne	0	0	0	1	0	1	0	0	0	2
Encephalitis lethargica	0	0	0	0	0	10	1	0	0	11
Hirntumor	1	0	1	2	0	4	2	0	0	10
Geisteskrankheit	4	1	9	8	19	32	20	2	1	96
Schwachsinnige-Zurückgebliebene	0	0	0	0	7	7	8	0	1	23
Summe	6	3	17	19	38	89	38	3	7	220

liche Faktoren eine entscheidende Rolle bei der Entstehung der Krankheit spielen.

Voss, der systematische anamnестische Studien über die multiple Sklerose durchführte, ist demgegenüber zu der Auffassung gelangt, dass die erbliche Belastung bei der multiplen Sklerose den Durchschnitt sicherlich nicht überschreitet.

Neulich beschreiben *Fog* und *Winther* einige Fälle von familiärer multipler Sklerose. Bei *Winther's* sämtlichen drei Fälle handelt es sich um Geschwister.

Zusammenfassend wird man sagen können, dass also multiple Sklerose in der Verwandtschaft des Erkrankten vorkommen kann. Ein Teil der Forscher nimmt sogar an, dass die Krankheit in diesem Fall in einer Proportion vorkommen würde, die grösser als die Frequenz der Krankheit in der übrigen Bevölkerung ist.

Bei dem von mir untersuchten Material fand ich multiple Sklerose in der Familie des Erkrankten in 19 Fällen. Die hier berücksichtigten Familienfälle können als sichere Fälle von

multipler Sklerose angesehen werden; sie sind alle in Krankenhäusern diagnostiziert. Die Verteilung dieser Fälle innerhalb der Verwandtschaft des Patienten geht aus der Tabelle 14 hervor. Die 2 Fälle, die dort unter der Rubrik »In der Verwandtschaft« aufgenommen wurden, beziehen sich beide auf Schwäger der Patienten und sind deshalb nicht durch irgendein Blutband mit dem Kranken verbunden. Sie müssen bei der Studie familiärer Belastung weggelassen werden, aber sie sind doch von Bedeutung bei der Diskussion über die infektiöse Genesis.

In 4 Fällen kam die Krankheit bei Schwestern vor, in 5 Fällen bei Brüdern, in 6 Fällen bei Schwester und Bruder und in den zwei verbleibenden Fällen bei Tochter und Vater und Mutter. Wenn wir das Vorkommen in der engeren Familie mit 17 Fällen rechnen und diese Zahl in Verhältnis setzen zu der Anzahl von Fällen des Materials, in denen sichere Angaben über die familiären Krankheiten erhalten werden konnten, d. h. zu 1015 Fällen, so ergibt sich die Zahl von  $1,68\% \pm 0,4$ . Das Vorkommen der multiplen Sklerose innerhalb der Gesamtbevölkerung beträgt 1365 Fälle auf 6 141 571 Einwohner, das heisst also nur  $0,0223\% \pm 0,0005$ . Genau wie *Bing* und *Curtius* habe also auch ich eine grössere Frequenz der multiplen Sklerose innerhalb der Familien der Kranken festgestellt als sie sich innerhalb der Gesamtbevölkerung findet, und zwar ist dieser Unterschied etwa 80 mal so gross ( $e(D) = 1,66 \pm 0,4$ ).

Diese Zahlen gelten nur für die sicheren Fälle von multipler Sklerose. In einer keineswegs geringen Anzahl der Fälle haben die Patienten aber teils in den Krankenhausejournalen teils in Angaben an mich auf Grund der Fragebogen angegeben, dass gewisse Angehörige an Krankheiten gelitten hätten, die ihrer eigenen geglichen. Unzweifelhaft handelt es sich hierbei in einer Mehrzahl von Fällen wahrscheinlich nicht um multiple Sklerose, sondern um andere Nervenkrankheiten, aber ebenso sicher ist, dass zumindest in einem Teil der Fälle wirklich die Rede von multipler Sklerose gewesen ist. Also auch wenn diese Fälle diagnostisch nicht sichergestellt sind, so haben sie doch vom hereditären Gesichtspunkt aus ihr grosses Interesse, als neurogene Belastung. Die Verteilung der verschiedenen Fälle kann in der Tabelle 14 abgelesen werden.

Nachstehend eine Analyse dieser Fälle:

In 8 Fällen war die Diagnose Rückenmarksleiden. In einem Fall hatte der Bruder der 20 jährigen weiblichen Patientin ähnliche Symptome mit unsicherem Gang und Sehstörungen. In einem Fall war der Vater eines 50 jährigen männlichen Patienten zunächst an einer Hand gelähmt worden, später an den Beinen und danach an seiner Krankheit verstorben. In einem Fall hatte der Bruder einer 47 jährigen Frau an schwankendem Gang mit Schütteln in den Beinen gelitten, später traten Gehstörungen hinzu, so dass er die letzte Zeit nicht mehr gehen konnte. In so gut wie allen anderen Fällen ist von den Kranken angegeben worden, sie hätten die gleichen oder ähnliche Krankheitssymptome gehabt wie die Patienten, aber ohne andere Details.

Es hat also den Anschein, dass die Ziffer, die ich mit 1,68 % oben für das Vorkommen der multiplen Sklerose innerhalb der Familien angab, eher zu niedrig gegriffen ist, weil auch ein Teil der eben wiedergegebenen Fälle multiple Sklerose gewesen sein kann. Die Belastung würde auf diese Weise noch intensiver werden und beachtlich die von den oben genannten Forschern angegebene übertreffen.

Durch die Untersuchungen von insbesondere *Curtius* wurde aufgezeigt, dass Nerven- und Geisteskrankheiten ebenso wie rudimentäre Formen derselben bedeutend häufiger bei Familienmitgliedern von Patienten mit multipler Sklerose auftreten als bei der Durchschnittsbevölkerung. *Curtius* ist der Auffassung, dass die Eltern solcher an multipler Sklerose leidender Patienten sich von der Durchschnittsbevölkerung insoweit deutlich unterscheiden, als sie als ausgesprochen psychisch minderwertig zu bezeichnen seien. Bei den Geschwistern der Kranken fand er nicht die gleiche Minderwertigkeit, glaubt aber, dass dies darauf beruhe, dass diese zur Zeit der Untersuchung sich noch in recht jugendlichem Alter befunden hätten. Er weist auch darauf hin, dass das Vorkommen organischer Nervenkrankheiten neben verschiedenen Psychopathien eine gesetzmässige Erscheinung sei.

*Schaltenbrand* hat ebenso wie *Curtius* dieselben neuropathologischen Dispositionen in Familien, in denen die multiple Skle-

rose vorkommt, gefunden. So hat er in solchen Familien sowohl Muskeldystrophien als auch Friedreichs Ataxie gesehen. Trotzdem ist er der Ansicht, dass diese Verhältnisse den erblichen Charakter der Krankheit nicht beweisen, dass dies vielmehr nur eine gewisse Geneigtheit im Nervensystem bei diesen Familien andeute. Eine vergleichbare Geneigtheit findet man bei Patienten, die an Tabes oder Paralyse erkranken (*Schaltenbrand*).

Auch *Marburg* meint, dass bei nervös Belasteten, bei denen eine gewisse Schwäche in der Anlage des Nervensystems vorausgesetzt werden kann, die Krankheit sich unter Umständen leichter entwickeln kann. Indessen glaubt er nicht, dass dies mit Notwendigkeit für die endogene Genese der multiplen Sklerose spricht.

Ich habe bei meinem Material versucht auch auf die eventuelle Belastung mit Nerven- und Geisteskrankheiten überhaupt gesehen Rücksicht zu nehmen, so dass man aus der Tabelle 14 das Vorkommen von Epilepsie, Migräne, Encephalitis lethargica, Hirntumoren, Geisteskrankheiten und Schwachsinn oder Zurückgebliebenheit in den Familien der Erkrankten ansehen kann. Am meisten überrascht hierbei die ungewöhnlich hohe Zahl von Fällen von Geisteskrankheit in der Verwandtschaft der an multipler Sklerose erkrankten Patienten. Die Gesamtzahl beträgt 96, und von diesen sind die Mehrzahl entsprechend den gemachten Angaben in Irrenanstalten behandelt worden. Die Grösse und Bedeutung dieser Ziffer zu beurteilen ist schwierig. Vergleicht man das Vorkommen der Geisteskrankheiten innerhalb der Bevölkerung überhaupt — berechnet für 1920, wo 15 556 Geisteskranke auf 5 904 000 Einwohner oder 0,27 % kamen — mit dem Vorkommen von Geisteskranken in den Familien der an multipler Sklerose Erkrankten — also 96 Geisteskranke auf 1010 Fälle von multipler Sklerose oder fast 9,6 % —, so findet man für die letztere Gruppe eine bedeutend grössere Frequenz dieser Krankheiten. Wenn auch natürlich diese Zahlen nicht unmittelbar vergleichbar sind — umfasst die eine doch eine Periode eines Jahres und die andere eine solche von 10 Jahren —, so geben sie doch eine ungefähre Auffassung der Verhältnisse.

Studiert man die ganze nenro-psychogene Belastung, so findet man also innerhalb des vorliegenden Materials in nicht we-

niger als 220 Fällen familiäres Vorkommen neuro-psychogener Krankheiten. Relatiert man diese Ziffer auf das ganze Material der multiplen Sklerose (1365 Fälle) bekommt man 16 %. Irgend eine Auskunft über das Vorkommen dieser Krankheiten unter der Bevölkerung des ganzen Landes habe ich nicht erhalten können, aber es scheint wahrscheinlich, dass die von mir erhaltene Ziffer ungewöhnlich hoch ist.

*ZUSAMMENFASSUNG: Die Untersuchung hat gezeigt, dass in Familien von Patienten, die an multipler Sklerose leiden die multiple Sklerose nahezu 80 mal so oft vorkommt wie in der Durchschnittsbevölkerung. Die erhaltene Ziffer liegt sogar an der Unterseite weil sich innerhalb des Materials eine Anzahl von Fällen findet, die nicht mit Sicherheit verifiziert werden konnten, bei denen aber die Diagnose der multiplen Sklerose möglich ist. Auch das Vorkommen von Geisteskrankheiten in den Familien der Patienten mit multipler Sklerose ist bedeutend grösser als bei der normalen Bevölkerung. Die ganze neuro-psychogene Belastung geht bis 16 % hinauf.*

## 2.) Tuberkulose bei multipler Sklerose.

Bei der Diskussion über die Ätiologie der multiplen Sklerose ist in neuerer Zeit auch die Frage nach der Bedeutung der Tuberkulose für die Entstehung der Krankheit aufgeworfen worden. Durch Marburgs und Löwensteins Entdeckung von Tuberkelbacillen im Blute eines an multipler Sklerose Erkrankten wurde die Tuberkulose rein zufällig in den Vordergrund des ätiologischen Resonnemangs geschoben. Später glückte es Löwenstein bei 17 von 40 Fällen multipler Sklerose Tuberkelbacillen im Blut anzuzeigen.

Bald fand man jedoch, dass Tuberkelbacillämie bei mehreren verschiedenen Krankheitszuständen vorkommen konnte, so auch bei den verschiedensten Nerven- und Geisteskrankheiten. Den sporadischen Funden von Tuberkelbacillen im Blut von Patienten mit multipler Sklerose hat daher keine ätiologische Bedeutung zugemessen werden können.

Trotzdem wollte man den Gedanken eines ätiologischen Zusammenhanges zwischen den beiden Krankheiten nicht fallen

lassen. So nimmt *Friedinger* nach wie vor an, dass es einen Zusammenhang zwischen Tuberkulose — dabei auch Scrofulose — gibt. Die gleiche Ansicht wird von *Ahringsmann* verfochten, der in mehreren Arbeiten eine Theorie vorlegte, dass die multiple Sklerose eine Form der Metatuberkulose im Centralnervensystem sein dürfte. Er zieht auf solche Weise Parallelen zwischen der multiplen Sklerose und den metalnetischen Veränderungen im Nervensystem. Seine Theorie ist auf starken Widerstand gestossen und er verteidigt sie daher in einer 1938 herausgekommenen Arbeit. In ihr setzt er die Frequenzerhöhung der multiplen Sklerose in Zusammenhang mit der Tatsache, dass die Tuberkulosemorbidity nach dem ersten Weltkrieg und in den darauffolgenden Jahren ganz besonders zunahm. Wenn man für das Entstehen von Metakrankheiten ein Intervall von ca. 10 Jahren berechnet, muss man — sagt *Ahringsmann* — also die Zahl der Fälle von multipler Sklerose nach etwa 1928 erhöht bekommen. Das ist auch geschehen. Die grösste Lücke seiner Theorie erblickt er selbst darin, dass es bisher weder ihm noch anderen gelungen ist Tuberkelbacillen\* in diesen metatuberkulösen Veränderungen nachzuweisen.

Die Angaben, die über das Verhältnis zwischen Tuberkulose und multipler Sklerose erhalten werden können, sind wenig zahlreich und die Ansichten gehen auseinander und stehen sich gegenüber. Daher ist es nicht einfach an das Centrale des Problems zu kommen. Für eine derartige Untersuchung eignet sich mein Material auch nicht. Das einzige, was im vorliegende Material zu beurteilen möglich ist, ist das Vorkommen der Tuberkulose bei den Patienten selbst und innerhalb deren Familie. Aber diese Details führen uns nicht zum Kernpunkt des Problems. Dennoch ist es möglich, dass aus ihnen ein Teil wertvoller Anhaltspunkte gewonnen werden können, die die Frage der Bedeutung der Tuberkulose bei Erforschung der multiplen Sklerose beleuchten.

Soweit dies möglich, ist mein Material auf familiäres Vorkommen von Tuberkulose hin untersucht. In dem Fragebogen, der an sämtliche Patienten herausgesandt wurde, wird das Vorkommen von Tuberkulose, sowohl bei den Patienten selbst (Lungentuberkulose, Pleuritis, Erythema nodosum, Scrofulose),



Tuberkulose ist nämlich nicht die gleiche auf dem Lande, wie in der Stadt, auch variiert ihre Frequenz für die verschiedenen Teile des Landes. Ein Material, das auf die geographisch-pathologischen Verhältnisse Rücksicht nimmt, wurde von *Uddströmer* aufgestellt. Er untersuchte das familiäre Vorkommen der Tuberkulose bei Schnlkindern teils in Stockholm, teils in einigen Orten der Bezirke Kalmar und Gävleborg. Sein Material umfasst 700 Fälle, für die er eine familiäre Belastung mit Tuberkulose von 29 % findet. Die Angaben, die *Uddströmer* hinsichtlich der Heredität erhielt, umfassen dieselben Familiengruppen, die ich in meine Tabellen aufnahm. Verglichen mit diesem Material gesunder Individuen und deren Verhältnis zur Tuberkulose, zeigt mein Material nach jeder Richtung keine irgendwie erhöhte familiäre Belastung für Tuberkulose. Die normale Variation liegt hier zwischen 17—29 % und die Frequenz meines Materials bleibt ja unter 20 %. Zur Erklärung meiner niedrigen Ziffer möchte ich darauf hinweisen, dass meine Patienten in grösserem Ausmass vom Lande stammen und dass es sich ausserdem gezeigt hat, dass die multiple Sklerose in den Bezirken nicht so gewöhnlich ist, in denen Tuberkulose am häufigsten vorkommt. Auf diese Sachlage werde ich in einem späteren Kapitel noch zurückkommen.

*ZUSAMMENFASSUNG: Aus der Untersuchung geht hervor, dass sich bei den Patienten mit multipler Sklerose keine erhöhte familiäre Belastung mit Tuberkulose findet. Auch sind diese Patienten selbst nicht in grösserem Ausmass der Erkrankung an klinisch manifestierbarer Tuberkulose ausgesetzt.*

#### *f) Dauer und Sterblichkeit.*

Von den 1365 Fällen des Materials sind nach den Angaben, die ich von den Patienten erhalten konnte, nunmehr 339 verstorben, d. h. nahezu 25 %. Ich habe in meiner Statistik der Mortalität alle angegebenen Toten berücksichtigt. Gewöhnlich verstirbt ein Patient mit multipler Sklerose nicht unmittelbar an der multiplen Sklerose als solcher sondern an irgend einer komplizierenden Krankheit. Es war unmöglich exakter die Patienten, die an multipler Sklerose verstorben sind, von denen zu trennen, die an irgend einer interkurrenten Krankheit star-

ben. Daher war ich gezwungen bei der Behandlung der Frage der Mortalität der multiplen Sklerose sämtliche Toten zu berücksichtigen. In 15 Fällen war die Todesursache als Komplikation der multiplen Sklerose etwas ungewöhnlicher, nämlich in 5 Fällen Herzkrankheit, in 4 Fällen Embolien, davon in 2 Fällen nach Partus, in 3 Fällen Cancer und in jeweilig einem Fall Urämie, Tuberkulose und akute Polyarthrit.

Die hauptsächliche Korrespondenz mit den Patienten war bereits um 1938 abgeschlossen. Nach diesem Zeitpunkt sind nur noch Kompletierungen ausgeführt worden. Mit der überwiegenden Mehrzahl der Patienten bin ich also bis 1938 in Kontakt geblieben, nach dieser Zeit nur mit einigen Hundert. Deshalb wurden die meisten Angaben über Tote für die Zeit von 1925—1937 erhalten. Sicherlich sind seit dieser Zeit eine nicht geringe Anzahl von Patienten mit multipler Sklerose darüber hinaus verstorben und die angegebene Ziffer von 339 dürfte in Wirklichkeit bedeutend grösser sein.

Tabelle 18. Anzahl der Patienten mit multipler Sklerose, die während der Jahre 1925—1936 verstarben.

	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	Summe
Frauen	4	10	5	10	12	8	21	21	15	20	20	21	167
Männer	2	4	4	7	8	11	13	14	20	11	13	17	124
Summe	6	14	9	17	20	19	34	35	35	31	33	38	291

Aus Tabelle 18 kann man entnehmen, wie etwa seit 1931 die Zahl der Toten sich jährlich um ungefähr 34—38 bewegt. In den früheren Jahren ist die Mortalität niedriger. Dies Verhältnis steht natürlich im Zusammenhang mit der Dauer der Krankheit, die in meinem Material, die ich weiter unten ausführen werde, in Mittel bei ungefähr 9 Jahren liegt. Nach dem vorliegenden Material zu urteilen, versterben also jährlich etwa 35 Personen mit multipler Sklerose.

Im Zusammenhang mit der Mortalität habe ich die Frage nach der Dauer der Krankheit behandelt. Die multiple Sklerose führt ja früher oder später stets zum Tode und daher entspricht die Dauer der Krankheit der Zeit vom Beginn der Erkrankung

bis zum Eintritt des Todes, ausgenommen natürlich die wenigen Fälle, in denen eine von der multiplen Sklerose nicht bedingte Krankheit das Leben des Patienten endigt. Mit der grösstmöglichen Genauigkeit habe ich bei meinem Material das Erkrankungsalter versucht zu bestimmen.

Die Berechnung der Duration ist mit den gleichen Fehlerquellen belastet, wie die Bestimmung der Mortalität, nämlich damit, dass die Patienten an einer Krankheit verstorben sein können, die in keiner Weise mit ihrer multiplen Sklerose zu tun hatte. Dennoch dürfte die Anzahl dieser Patienten gering sein.

Die Dauer konnte in 285 Fällen berechnet werden. Bei diesen konnte das Erkrankungsalter einigermaßen mit Sicherheit bestimmt werden.

Tabelle 19. Dauer der multiplen Sklerose bei verschiedenem Erkrankungsalter in Jahren ausgedrückt.

Erkrankungsalter	Anzahl der Fälle	Dauer nach Jahren		Mittelzahlen M	$\delta$	e(M)
		mindestens	höchstens			
10—14	16	1	29	9,9	$\pm 3,6$	$\pm 0,9$
15—19	30	1	41	10,7	$\pm 3,7$	$\pm 0,7$
20—24	49	3	39	13,0	$\pm 0,1$	$\pm 0,01$
25—29	55	1	36	9,2	$\pm 1,4$	$\pm 0,2$
30—34	42	1	31	9,5	$\pm 2,7$	$\pm 0,4$
35—39	31	1	25	8,7	$\pm 1,6$	$\pm 0,3$
40—44	30	1	17	7,3	$\pm 1,9$	$\pm 0,3$
45—49	12	1	23	8,1	$\pm 2,7$	$\pm 0,8$
50—54	15	1	16	7,7	$\pm 1,0$	$\pm 0,3$
55—59	5	1	8	5,6	$\pm 0,8$	$\pm 0,4$
S u m m e	285			9,2	$\pm 4,1$	$\pm 0,2$

Aus der Tabelle 19 kann man entnehmen, dass die multiple Sklerose im Mittel sich über eine Zeitspanne von 9 Jahren erstreckt, aber auch, dass sie in extremen Fällen innerhalb eines Jahres zum Tode führen kann, oder bis an 41 Jahre heranreicht. Ein auffallenderer Unterschied der Dauer im Verhältnis zum Erkrankungsalter kann nicht aufgezeigt werden.

Die Dauer der multiplen Sklerose wird von den verschiedenen Forschern recht verschieden angegeben. *Marburg*, der durch *Zellmann* die Dauer der multiplen Sklerose in 50 Fällen untersuchen liess, kommt zu dem Schluss, dass die gewöhnliche Dauer 2—4 Jahre beträgt, dass jedoch vereinzelte Individuen nach dem Beginn der Krankheit bis zu 30—35 Jahren leben könnten. *Brain* teilt eine Durationsvariation von einigen Monaten bis zu 30 Jahren mit und *Bramwell* gibt für 36 Fälle mit tötlichem Ausgang eine Mittelzahl von 8 Jahren. *Drobnes*, der 114 Patienten mit multipler Sklerose nachuntersuchte, wovon 46 verstarben, bezeichnet die Durchschnittsdauer mit 12,5 Jahren.

ZUSAMMENFASSUNG: *Die Mortalität des untersuchten Materials beträgt 25 %, was etwa 35 Personen jährlich beträgt. Die Dauer der Krankheit ist mit 9 Jahren im Mittel berechnet worden.*

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### 3. Kapitel.

#### *Das geographische Vorkommen.*

##### *1. Einleitung. Multiple Sklerose in den Städten und auf dem Lande.*

Für die Studie über das Vorkommen der multiplen Sklerose und ihre Ausbreitung innerhalb Schwedens ver füge ich über 1365 Fälle. In den vorhergehenden Kapiteln habe ich dieses Material eingehend beschrieben und die Mängel aufgezeigt, die einem solchen Material unzweifelhaft anhaften. Die grössten Schwierigkeiten beim Erhalten eines guten und anwendbaren Materials von multiplen Sklerosefällen waren die richtige Stellung der Diagnose und die Bestimmung des Beginns der Krankheit. Liegt es doch in der Natur der multiplen Sklerose, dass man oft erst nach langjähriger Verfolgung der Krankheit und ihrer Entwicklung zu einer einiger massen sicheren Diagnose gelangt, und der Zeitpunkt des Beginns der Erkrankung ist keineswegs immer so ausgeprägt, dass er mit Sicherheit wahrgenommen wird. Um diese Mängel soweit wie möglich auszugleichen, habe ich, wie oben eingehend beschrieben worden ist, durch einen Schriftwechsel mit den Patienten die Punkte noch weiter zu klären versucht, die hier von Interesse sein können. Gerade die oben letztgenannte Schwierigkeit, die Bestimmung des genauen Zeitpunktes des Erkrankens, ist erklärlicher Weise von grosser Wichtigkeit, wenn es sich darum handelt, die Kranken an verschiedenen Stellen des Landes zu lokalisieren, denn die Kranken sind immer an diejenige Ort lokalisiert geworden, wo sie wahrscheinlicher Weise an ihrer multiplen Sklerose erkrankten. Auf Grund des Schriftwechsels hat sich die Anzahl der Fälle von multipler Sklerose, die innerhalb des Landgebiets lokalisiert werden können, etwas verringert. Es stellte sich nämlich heraus, dass in 23 Fällen die Patienten im Auslande erkrankt waren und

daher natürlich nicht in die geographische Lokalisierung aufgenommen werden konnten. 13 dieser Fälle waren in den USA, 2 in Kanada, 2 in Finnland und Norwegen und je 1 in Dänemark, Deutschland, England und Holland erkrankt.

Ein weiterer Faktor, der darüber hinaus das Material reduzierte, war, dass die Patienten in 36 Fällen keine irgendwie geartete feste Wohnung hatten, sondern mit nur kurzem Aufenthalt von einem zum anderen Platz zogen — ein oder zwei Jahre betrug im Durchschnitt die Sesshaftigkeit — oder, wie in einer kleinen Zahl von Fällen, überhaupt einer festen Wohnungsanschrift ermangelten.

Sonach gehen von den 1365 Fällen 23 ab, die ausser Landes erkrankten, und 36, die nicht sicher lokalisiert werden können, und es verbleiben für die geographische Lokalisation meines Materials an multiplen Sklerosefällen 1306 Fälle.

Von diesen 1306 Fällen waren 392 (30 %) in Städten ansässig und 914 (70 %  $\pm 1,3$ ) auf dem Lande. 1931 waren in Schweden 2 034 353 (33 %) Individuen in Städten ansässig und 4 128 093 (67 %  $\pm 0,02$ ) auf dem Lande. Die Ziffern geben zwar ein unbedeutendes Übergewicht der Landbewohner an, das doch geringfügig und nicht statistisch feststellbar ist. ( $e(D) = 3 \pm 1,265$ ).

	Einwohner- zahl	Anzahl der Fälle von multipler Sklerose	Frequenz pro 10 000 Einwohner	Durchschnitt- licher Fehler für die Frequenz
Städte	2 034 353	392	1,92	$\pm 0,095$
Land	4 128 093	914	2,21	$\pm 0,072$

In der Litteratur findet man angegeben, dass die multiple Sklerose etwas häufiger in den Städten vorkommen soll, als auf dem Lande. Solche Angaben machen *Davenport, Koch* und *Brain*. *Koch* macht allerdings darauf aufmerksam, dass, auch wenn die Frequenz in den Städten proportional grösser wäre, doch die grössere Mehrzahl der Patienten mit multipler Sklerose auf dem Lande geboren seien. *Steiner*, der diese Verhältnisse ebenfalls erforscht hat, meint, dass das Übergewicht auf seiten der Stadt-

bevölkerung so gering wäre, dass es ohne Bedeutung sei und wahrscheinlich nur dadurch bedingt wäre, dass die Stadtbevölkerung es leichter habe ein Krankenhaus aufzusuchen als die Landbevölkerung. Meine Untersuchung hat ein etwas abweichendes Resultat gezeitigt, indem sich ein unbedeutendes Übergewicht der Landbevölkerung ergibt. Sie stimmt aber einigermaßen mit *Kochs* Auslassung überein, dass die Mehrzahl der Patienten mit multipler Sklerose auf dem Lande geboren sind.

Von den 914 auf dem Lande ausässigen Patienten waren 761 immer oder zumindest mehr als 10 Jahre vor Ausbruch der Krankheit an der Stelle ansässig gewesen, wo sie erkrankten, was einem Prozentsatz von 83 % entspricht. Dieselbe Ziffer für die Städter beträgt 240 Patienten oder 61 %. Die an den verschiedenen Plätzen lokalisierten Personen haben also in stärkster Masse so gut wie ständig bereits an dem Platz gewohnt, den sie bewohnten, als sie von der Krankheit befallen wurden.

Ein eingehenderes Studium des Verhältnisses zwischen eingeborenen und zugezogenen Kranken zeigt folgendes Bild: Wenn man das Verhältnis zwischen eingeborenen und zugezogenen für die normale Bevölkerung berechnet, erhält man für die Stadt 0,745 und für das Land 1,365. Von den 392 Patienten, die in Städten wohnten und den 914, die auf dem Lande wohnten, hatten 179 bzw. 605 immer auf demselben Platz gewohnt, wo sie an ihrer multiplen Sklerose erkrankten. Es verblieben also 213 bzw. 309 zusammen 522 Fälle. Bei 195 dieser Fälle erhielten wir keine Antwort auf unsere Fragen. Werden diese Fälle abgerechnet, so erhält man für die Städte 133 und für das Land 261 zugezogene Patienten. Die Relation Eingeborene — Zugezogene beträgt also für die Städte  $179/133 = 1,346$  (gegen normal 0,745) und für das Land  $605/261 = 2,318$  (gegen normal 1,365). In beiden Fällen erhält man also deutlich höhere Werte als diejenigen sind, die für die normale Bevölkerung berechnet werden. Das ist ja diskutabel, wenn man, wie ich es hier getan habe, diejenigen abrechnet, die keine Antwort gaben. Eine nicht geringe Zahl von ihnen muss wohl zu den Zugezogenen gerechnet werden können, denn es liegt ja nahe anzunehmen, dass Patienten die ich weder brieflich noch durch das Pfarramt erreichen konnte, gerade solche sind, die oft ihren Aufenthaltsort

wechseln. Die ganze Anzahl Patienten ist aber nicht so gross, dass dies in höherem Grad das Ergebnis ändern kann.

Irgendein auffallender Unterschied zwischen den Verhältnissen auf dem Lande und in den Städten tritt in diesem Material nicht in Erscheinung.

Beitragend zu diesem Übergewicht, bei den Einheimischen an multipler Sklerose zu erkranken, erscheint mir, dass die Patienten zum grössten Teil in einem so zeitigen Alter an multipler Sklerose erkrankten, dass irgendein Wegzug vom Heimatort nicht mehr zustande kommt.

*ZUSAMMENFASSUNG: Für das Studium des geographischen Vorkommens der multiplen Sklerose innerhalb Schwedens disponiere ich über ein Material von 1306 Fällen von mit dem klinischen Bild übereinstimmender multipler Sklerose. Von diesen waren 392 in Städten ansässig und 914 auf dem Lande. Das Verhältnis zwischen den in den Städten ansässigen und den auf dem Lande wohnenden entspricht demjenigen für die normale Bevölkerung. Die Krankheit scheint in etwas höherem Grad die sesshafte Bevölkerung zu treffen.*

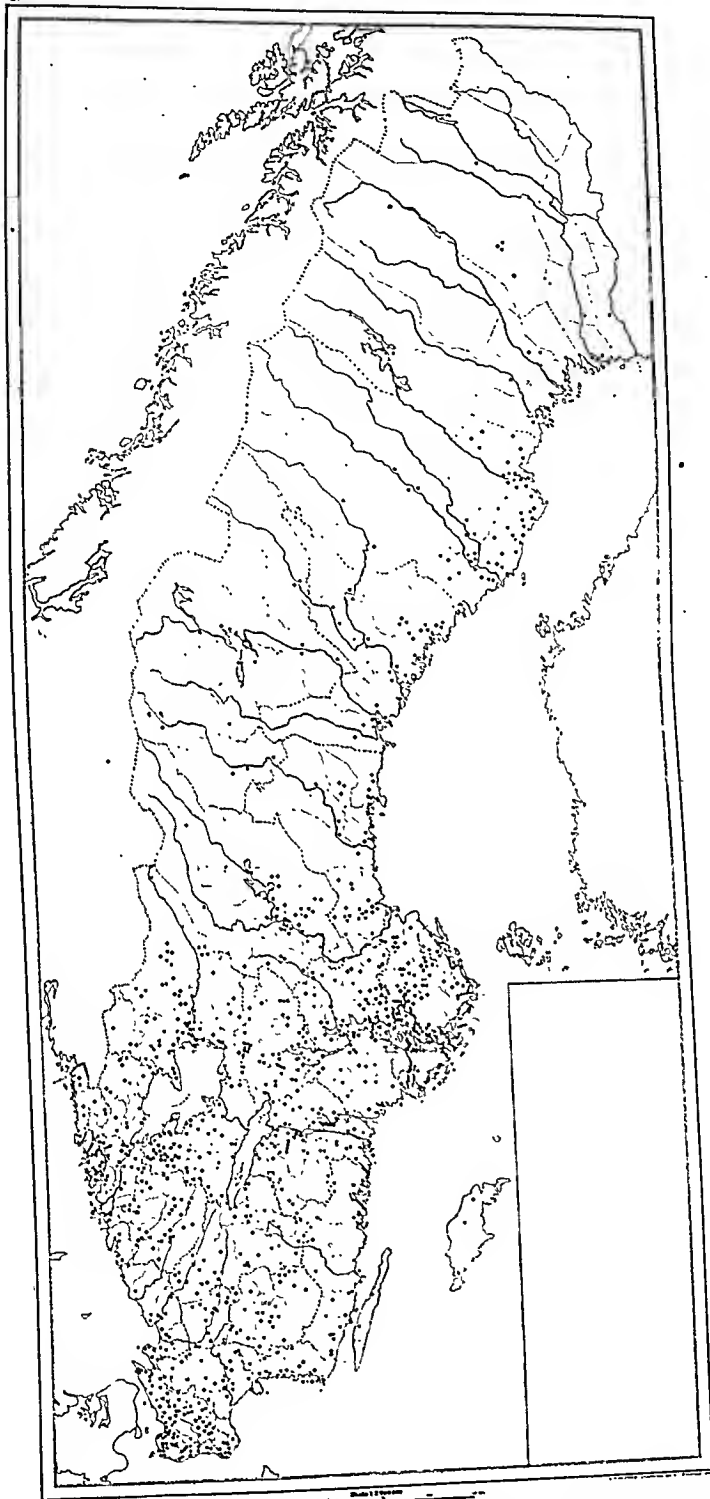
## 2. Die karthographische Erfassung und ihre Methode.

Die absolute Verteilung der Fälle mit multipler Sklerose — festgestellt, indem jeder einzelne Fall auf dem entsprechenden Platz, wo er erkrankte, eingepunktet wurde — zeigt, dass die multiple Sklerose im grossen gesehen über das ganze Land verteilt vorkommt. Auf der Karte der Figur 4 habe ich so gut, wie dies sich machen liess, auf einer Umrisskarte die verschiedenen Fälle dergestalt eingetragen, dass jeder Punkt einen Patienten bedeutet. Die Karte erfasst allerdings nur die 914 Fälle, die auf dem Lande erkrankt sind.

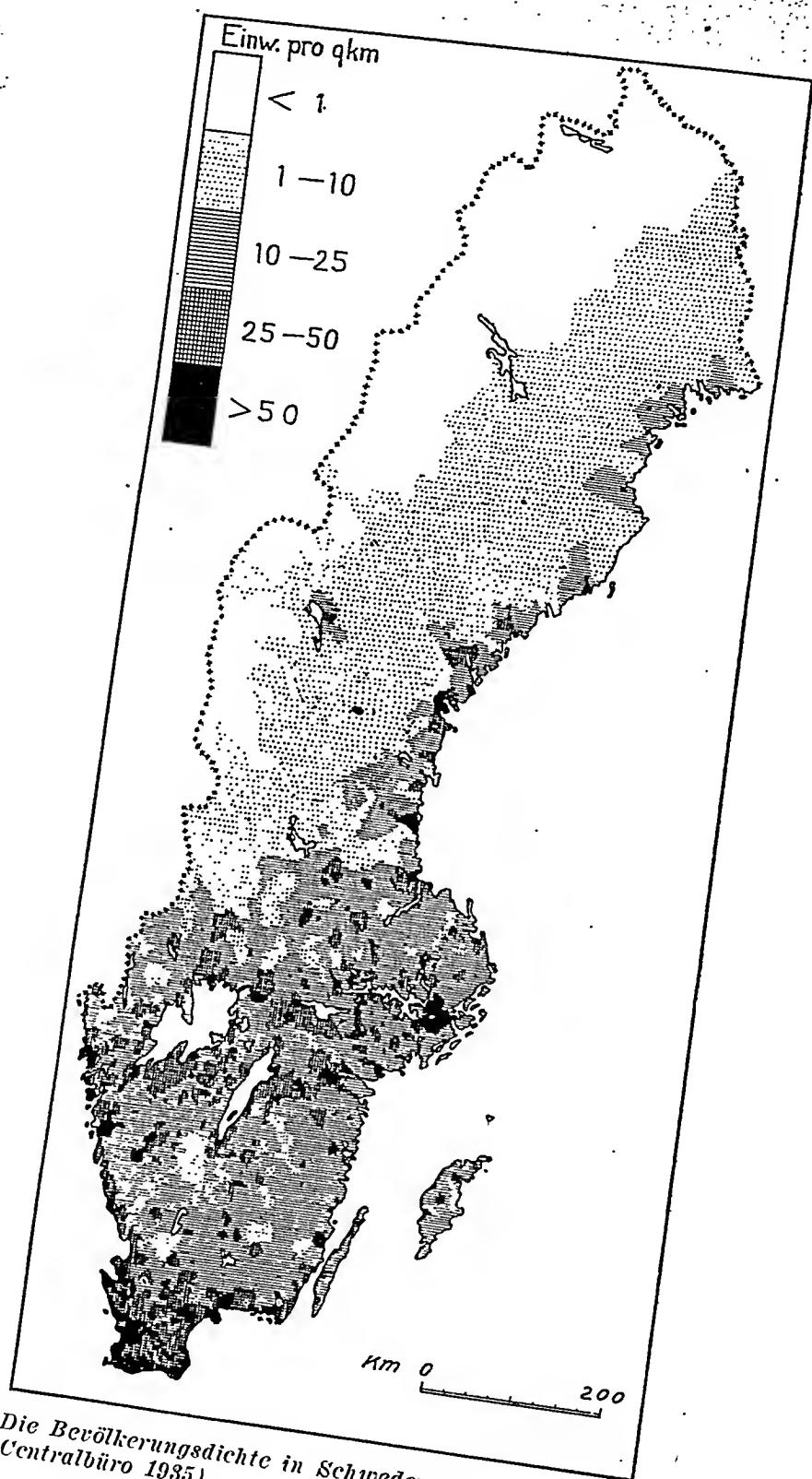
In Figur 5 wird eine Karte über die Bevölkerungsdichte in Schweden gegeben. Es zeigt sich unzweifelhaft eine gewisse Übereinstimmung zwischen grösserer Bevölkerungsdichte und einer erhöhten Anzahl von Fällen mit multipler Sklerose an vielen Stellen.

Sonach findet man im Allgemeinen zahlreiche Fälle innerhalb der volkreichen Gebiete. Doch scheint die Anzahl der Fälle innerhalb der relativ volkreichen Bezirke Södermanland und





Figur 4. Das Vorkommen der multiplen Sklerose innerhalb Schwedens während der Jahre 1925—1934. Jeder Punkt entspricht einem Krankheitsfall, ausserdem wurden in die Karte nur die auf dem Lande Erkrankten eingetragen (914 Fälle).



Figur 5. Die Bevölkerungsdichte in Schweden (1930). (Kgl. Statistisches Centralbüro 1935).

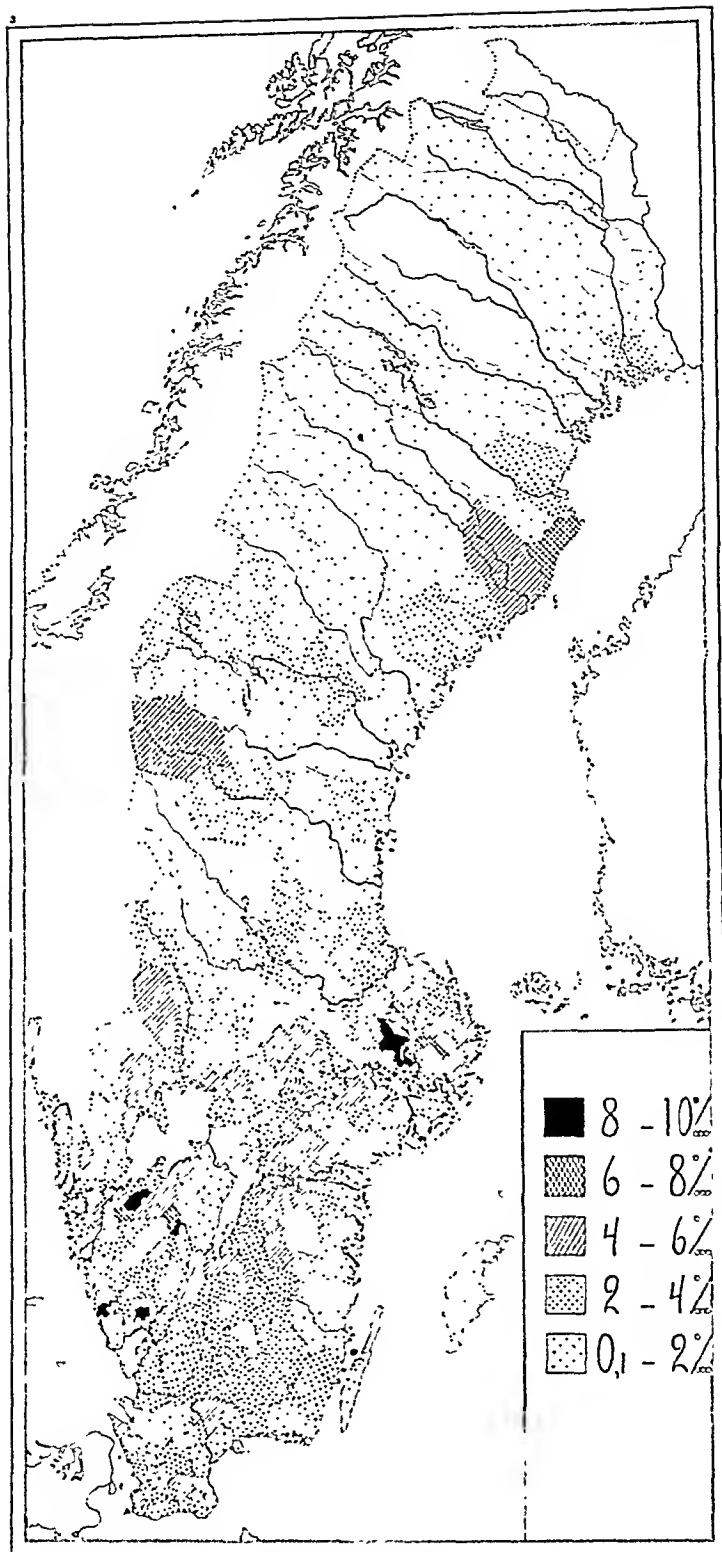
Kalmar proportional gesehen recht gering im Verhältnis zu Gegenden mit entsprechender Bevölkerungsdichte.

Von grösserer Bedeutung als das absolute Vorkommen ist indessen das Studium des relativen Vorkommens der Krankheit. Ebenso wie bei meiner früheren Arbeit über das Vorkommen der Thyreotoxikose innerhalb Schwedens habe ich das relative Vorkommen der multiplen Sklerose in verschiedenen administrativen Bezirken studiert. Zunächst habe ich, wie bereits im vorhergehenden Kapitel erwähnt, das Material in Fälle eingeteilt, die in den Städten lokalisiert sind, und in Fälle, die auf dem Lande angetroffen wurden. Dann wurde jede Gruppe für sich bearbeitet und nachher die Ergebnisse verglichen.

Was zuerst die Patienten des flachen Landes betrifft, so wurde deren relatives Vorkommen innerhalb der Kreise (*»Härad»*) und Gerichtsbezirke (*»Tingslag»*) berechnet d. h. die Fälle von multipler Sklerose wurde im Verhältnis zum Einwohnerzahl dieser Kreise berechnet und die Frequenz in Fällen pro 10 000 Einwohner angegeben. Am Schluss der Arbeit ist eine Tabelle der Zahlenwerte beigelegt, auf die sich diese Karte gründet. In Figur 6 eine so gezeichnete Karte.

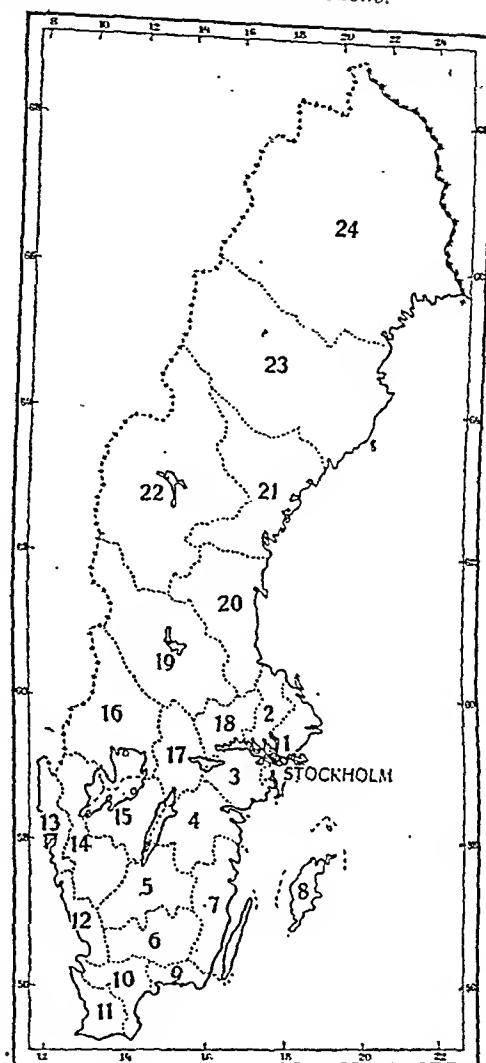
Die so gewonnene Karte bietet ein recht buntes Bild. Wenn man zunächst aber nicht an den kleineren Details haften bleibt, so wird man feststellen, dass eine reichlichere Frequenz der Krankheit hauptsächlich innerhalb folgender Regierungsbezirke wahrgenommen werden kann: Värmland, Skaraborg, Östergötland, dem östlichen Teil von Västmanland, Upsala, dem nördlichen Teil von Stockholm (Land), sowie in den Gegenden um Umeå und Skellefteå in Vasterbotten.

Eine Gegend mit höherer Frequenz findet sich auch im Regierungsbezirk Jämtland, hierbei bleibt aber zu beachten, dass diese Frequenz nur von 3 Fällen gebildet wird. Eine geringe Frequenz findet sich abgesehen von den eben erwähnten Gegenden um Umeå und Skellefteå und von Jämtland im grossen gesehen nördlich von Dalälv, eine frappierend kleine Frequenz haben wir im überwiegenden Teil von Stockholm-Land, dem Regierungsbezirk Södermanland und Kalmar, sowie an der Westküste in den Regierungsbezirken Kristianstad, Halland, Göteborg und Bohus.



Figur 6. Die Frequenz der multiplen Sklerose während der Periode 1925—1934 innerhalb grösserer administrativer Bezirke (Härad) markiert (914 Fälle).

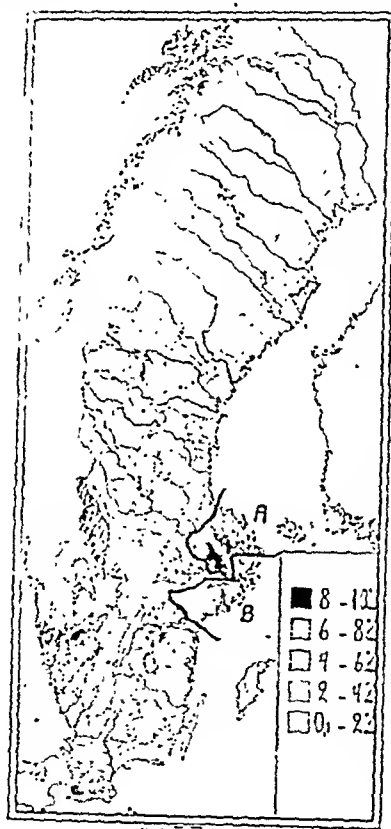
Figur 7. *Regierungsbezirke (Läne) Schwedens.*



- |                         |                               |
|-------------------------|-------------------------------|
| 1. <i>Stockholm</i>     | 13. <i>Göteborg und Bohus</i> |
| 2. <i>Uppsala</i>       | 14. <i>Älsborg</i>            |
| 3. <i>Södermanland</i>  | 15. <i>Skaraborg</i>          |
| 4. <i>Östergötland</i>  | 16. <i>Värmland</i>           |
| 5. <i>Jönköping</i>     | 17. <i>Örebro</i>             |
| 6. <i>Kronoberg</i>     | 18. <i>Västmanland</i>        |
| 7. <i>Kalmar</i>        | 19. <i>Kopparberg</i>         |
| 8. <i>Gotland</i>       | 20. <i>Gävleborg</i>          |
| 9. <i>Blekinge</i>      | 21. <i>Västernorrland</i>     |
| 10. <i>Kristianstad</i> | 22. <i>Jämtland</i>           |
| 11. <i>Malmöhus</i>     | 23. <i>Västerbotten</i>       |
| 12. <i>Halland</i>      | 24. <i>Norrbotten</i>         |

Die Frequenzzahlen und ihre Variationen sind nicht so bedeutend. Man fragt sich deswegen, ob man in die erhaltene Frequenzkarte grössere Gebiete auffinden kann, die miteinander vergleichen statistisch sichere Frequenzverschiedenheiten aufweisen. In Figur 8 habe ich auf die Frequenzkarte zwei verschiedene Gebiete mit ungefähr derselben Einwohnerzahl eingezeichnet, (die Städten nicht mitgerechnet), das eine mit grösserer Frequenz, den Bezirk Upsala und kleinere Teile der Bezirke Stockholm und Västmanland umfassend (A), das andere grösstenteils die Bezirke Stockholm und Södermanland umfassend (B).

Gebiet	Seine Einwohnerzahl	Anzahl Fälle multipler Sklerose	Frequenz 0/000	Durchschnittlicher Fehler für die Frequenz
A	220 618	88	3 986	$\pm 0,425$
B	225 083	22	0,977	$\pm 0,131$

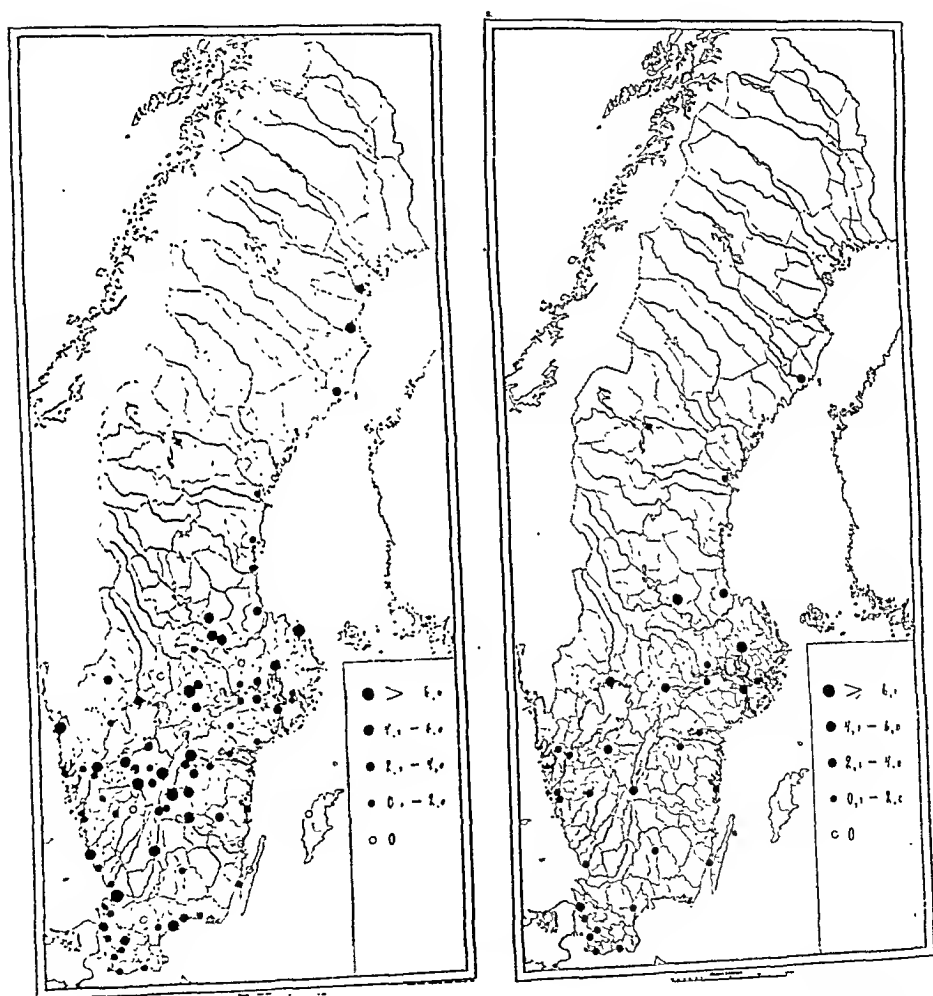


Figur 8.

Für beide Gebiete erhält man somit eine ausreichende Frequenzverschiedenheit. Der Durchschnittsfehler für die Differenz der Frequenzahlen ist  $3,011 \pm 0,46$  und somit statistisch sicher.

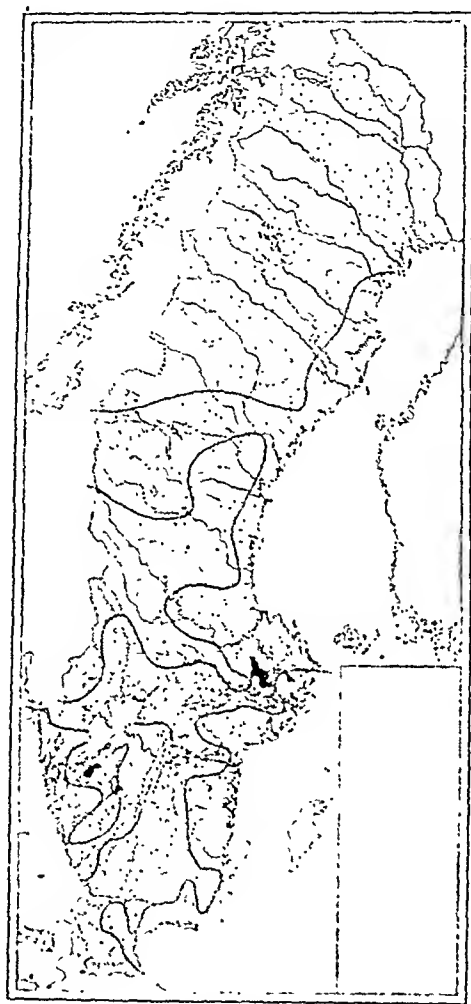
In der Figur 9 ist die Frequenz der multiplen Sklerose in den Städten eingezeichnet. Im grossen und ganzen entspricht die Frequenz in den Städten derjenigen auf dem Lande.

Blicken wir auf die Karte der Figur 9, auf der nur Städte mit 10 000 Einwohnern und darüber berücksichtigt sind — die Frequenz in den Kleinstädten mit ihren vereinzelt Fällen könnte nur irreführend sein —, können wir mindestens so viel sagen, dass die Städte mit höherer Frequenz sich sämtlich innerhalb der frequenzstarken Gebiete befinden. Es ergibt sich also eine Übereinstimmung zwischen der Krankheitsfrequenz in den Städten und derjenigen auf dem Lande.



Figur 9. Die Frequenz der multiplen Sklerose während der Jahre 1925—1934 in sämtlichen Städten Schwedens (392 Fälle) (links) und in Städten mit mehr als 10 000 Einwohnern (rechts).

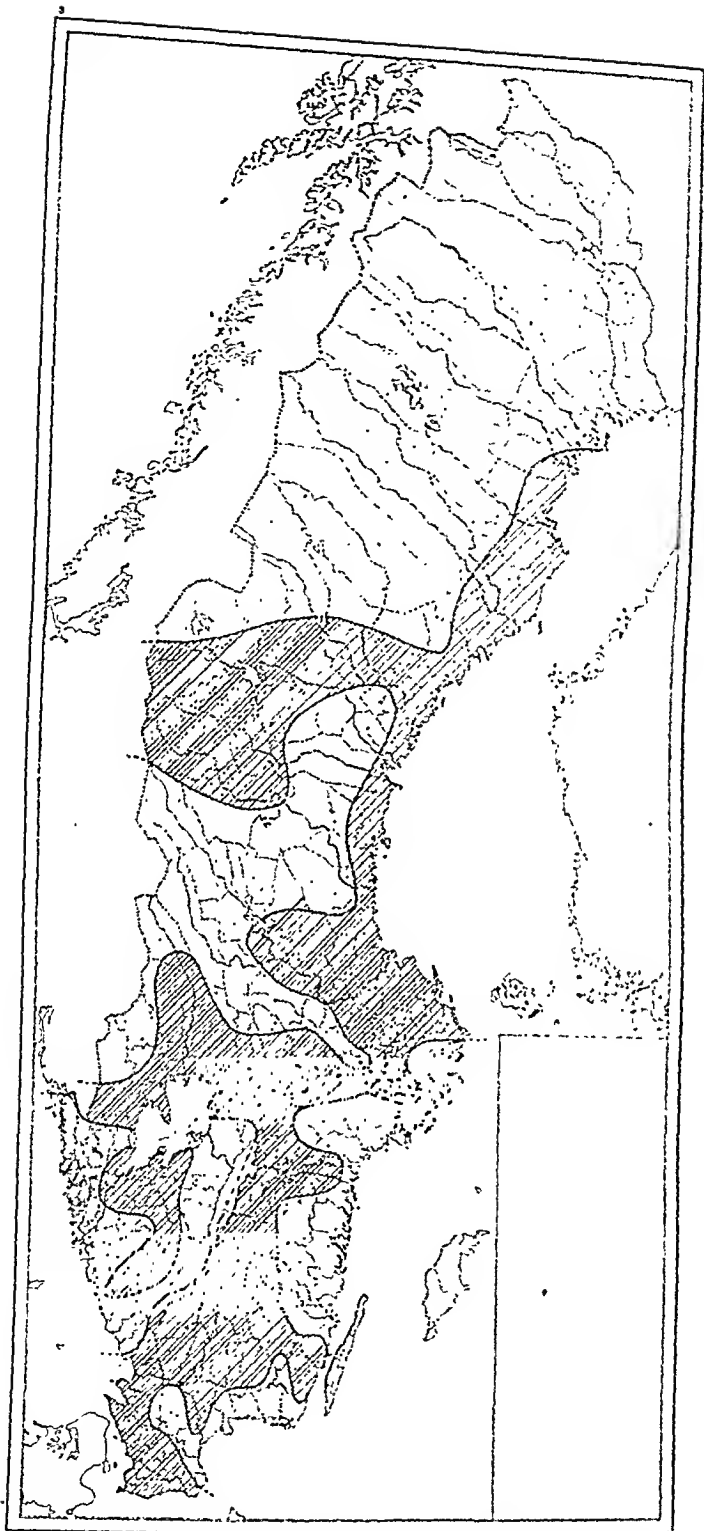
In der Karte der Figur 11 habe ich versucht das Vorkommen der multiplen Sklerose innerhalb des Landes zu generalisieren. Dabei habe ich mich nur zweier Frequenzbezeichnungen bedient, nämlich einer für reichliches und einer für geringes Vorkommen.



Figur 10.

In der Karte der Figur 10 habe ich die Grenzen zwischen den verschiedenen Frequenzbezirken eingezeichnet. Die Grenzen wurden teils aus der Karte der Regierungsbezirke entnommen, teils aus der Punktkarte und schliesslich noch auf Grund des Studiums über das Krankheitsvorkommen innerhalb der klein-





Figur 11. Übersichtskarte des Vorkommen der multiplen Sklerose, bei der unter Benutzung der vorangegangenen speciellen Karten die Frequenz der Krankheit in den einzelnen Bezirken und Städten generalisiert wurde.

sten Verwaltungseinheiten — der Kirchspiele. Es scheint mir überflüssig diese Karte in mehrere Frequenzen aufzuteilen, weil ja einmal die Zahl der Fälle, die lokalisiert wurden recht gering ist, zum anderen aber auch der Unterschied zwischen reichlicher und geringer Frequenz so unbedeutend ist, dass sich eine Aufteilung nicht lohnen würde.

Was die Verteilung der verschiedenen Krankheitstypen angeht, so möchte ich lediglich darauf hinweisen, dass die klassischen Fälle, die 5 % des ganzen Materials ausmachen (68 Fälle), keine spezielle Lokalisierung aufweisen. Ich habe gerade diese Tatsache mit einer gewissen Absicht herausgehoben, weil es ja denkbar wäre, dass die Diagnose multiple Sklerose in bestimmten Krankenhäusern lediglich auf die klassischen Fälle angewandt worden wäre, was sich jedoch als nicht zutreffend erwiesen hat. Klassische Fälle von multipler Sklerose wurden in etwa gleichem Ausmass in allen Krankenhäusern angetroffen. Daher haben sie auch keine spezielle geographische Lokalisation gezeigt.

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### *3. Auswertung des Ergebnisses der Karten über das Vorkommen.*

Auf Grund der Ergebnisse meiner Untersuchung muss als feststehend angenommen werden, dass die multiple Sklerose nicht in allen Teilen des Landes gleichmässig vorkommt, sondern innerhalb bestimmter Grenzen variiert. Man fragt sich, worauf diese Frequenzverschiedenheit beruht; veranlassen zufällige Faktoren sie oder hat die multiple Sklerose ein specielles geographisches Vorkommen?

Zunächst möchte ich erneut darauf hinweisen, dass jeder Fall, der in die Jahresberichte der Kgl. Medizinalverwaltung aufgenommen werden war, von mir nach den gleichen Prinzipien studiert und beurteilt wurde. In dieser Hinsicht ist das Material also gleichmässig.

Ein Umstand, von dem angenommen werden könnte, dass er zu der verschiedenen Krankheitsfrequenz der einzelnen Plätze

beigetragen hätte, könnte darin gesehen werden, dass die Bevölkerung möglicherweise innerhalb bestimmter Bezirke infolge stärkerer allgemeiner Morbidität dieser Gegenden häufiger das Krankenhaus aufsucht als dies in anderen Bezirken der Fall ist. Bei meiner früheren Untersuchung über das Vorkommen der Thyreotoxikose ist diese Frage eingehend studiert worden und festgestellt worden, dass die Bevölkerung in den verschiedenen Gegenden ungefähr in gleichem Anmass die Krankenhäuser aufsucht.

Ein anderer Faktor von Bedeutung ist die Wohnungslage des Patienten im Verhältnis zu derjenigen des Krankenhauses. Es wäre möglich, dass man eine reichlichere Verteilung der Krankheit im Umkreis der Krankenhäuser, Eisenbahnen und grösseren Landwege feststellte, weil die klinische Behandlung hier für den Patienten erleichtert ist. Ich habe eine so geartete Verteilung nicht gefunden.

Schliesslich muss wohl auch noch die Möglichkeit behandelt werden, dass ein Teil der Krankenhausärzte, die neurologisch ausgebildet oder interessiert sind, ein umfangreicheres Material von multipler Sklerose zusammengebracht haben würden, so dass aus diesem Grunde die Krankheitsfrequenz innerhalb verschiedener Bezirke entsprechend Knndschaft und Interesse für die Krankheit gewechselt haben dürfte. Ein solcher Gedanke liegt nahe, denn es handelt sich ja um eine Nervenkrankheit — wenn auch eine der häufigsten — und die Diagnose ist nicht selten schwer. Als ich zum ersten Mal meine Karte über das Vorkommen der Krankheit öffentlich vorlegte, wurde mir ein solcher Einwand entgegengehalten, und ich hielt es deshalb für erforderlich, diese Fehlerquelle im Interesse der Homogenität des Materials etwas eingehender zu überprüfen.

Eine Spezialklinik für Nervenkrankte findet sich nur in Stockholm und bereits hier kann man sehen, dass dies ohne Einfluss auf die Krankheitsfrequenz ist, denn sie ist gerade in Stockholm gering und auch in dem grösseren Teil des Stockholmer Regierungsbezirkes nicht gross. Ausser der Spezialklinik in Stockholm wurden während meiner Untersuchungszeit zumindest zwei neurologisch ausgebildete Chefärzte in Stockholm und einer in Mörby festgestellt.

In Upsala besteht ein Specialinteresse für Neurologie an der dortigen medizinischen Klinik und die dort vorliegende erhöhte Frequenz der Fälle könnte möglicherweise dadurch verursacht sein. Allerdings muss darauf hingewiesen werden, dass ein ganzer Teil der Fälle aus dem Upsalagebiet nicht von den Kliniken in Upsala geliefert wurden, sonder aus den Stockholmer Krankenhäusern und in vereinzelt Fällen aus Västerås und Gävle kamen.

Specialinteresse für Neurologie muss aber auch in Lund und Göteborg und seinen Kliniken angenommen werden. Im Gebiet um Lund ist demgegenüber die Frequenz nicht auffallend hoch, innerhalb der Göteborg umspannenden Gebiete ist sie dagegen klein und ebenso innerhalb der Stadt Göteborg. Die meisten Fälle von multipler Sklerose, die sich im västgötischen Gebiet lokalisieren stammen aus den Krankenhäusern der Städte in den Bezirken Älvsborg und Skaraborg. In den Krankenhäusern, wovon die meisten Fälle kommen, gibt es keine special ausgebildeten Neurologen. Seit 1931 wird die medizinische Klinik in Borås von einem neurologisch orientierten Chefarzt geleitet. Nach der Tabelle 1 bekommt man den Eindruck, dass etwa von 1930 ab eine Erhöhung der Fälle in Borås Platz greift. Bei näherer Analyse stellt man jedoch fest, dass mehr als 50 % der während dieser Zeit behandelten Fälle, ein oder mehrere Male im selben Krankenhaus oder in einem oder mehreren Krankenhäusern behandelt wurden.

Ein frequenzstarkes Gebiet findet man auch um Umeå und Skellefteå. In Umeå war 1925—1931 ein neurologisch orientierter Chefarzt an der medizinischen Klinik. Man kann jedoch nach seinem Weggang keine zuverlässige Verminderung der Fälle von multipler Sklerose feststellen. Ich will auch darauf hinweisen, dass die Anzahl der Fälle von Skellefteås bedeutend kleineren Krankenhauses proportional ziemlich gross ist. Auffallend ist auch, dass das Material aus Umeå in sehr grossem Umfang aus Fällen besteht, die zwei oder mehrmals im Krankenhaus (nahezu 70 %) behandelt wurden und dass daher die Zahlenwerte, die in der Tabelle 1 erscheinen bedeutend grösser sind als die Anzahl der Fälle in Wirklichkeit.

*Es scheint mir also bei näherer Erforschung der Verhältnisse, als ob die neurologische Ausbildung oder ein dahingehendes Interesse der jeweiligen Krankenhausärzte in keinem auffallenden Grad auf die Frequenz der multiplen Sklerose innerhalb der verschiedenen Gebiete eingewirkt hat.*

Als Kontrolle für die erhaltenen Karten habe ich einen Fragebogen an sämtliche Provinzärzte des Landes versandt und deren Ansicht über das Vorkommen der multiplen Sklerose erfragt. Dem Fragebogen wurde ungefähr die in Figur 6 wiedergebogen an sämtliche Provinzärzte des Landes versandt und de-

1. Findet sich innerhalb Ihres Distriktes multiple Sklerose?
2. Wieviele Fälle behandeln Sie jährlich innerhalb Ihres Distrikts?
3. Remittieren Sie die Fälle von multipler Sklerose, die Sie aufsuchen, ins Krankenhaus? Oder behandeln Sie sie zu Hause? Wieviele Fälle senden Sie jährlich auf diese Weise ins Krankenhaus?
4. Wieviel Einwohner hat Ihr Distrikt?
5. Entspricht die beigelegte Kartenskizze ungefähr dem Frequenzverhältnis, das Sie sich innerhalb Ihres Distriktes erwarten? Oder widerspricht sie Ihrer Auffassung über das Vorkommen der Krankheit und wenn ja, in welcher Beziehung?
6. Welche Prinzipien sind massgebend für Ihre Diagnose der multiplen Sklerose?

In einer Einleitung zu diesem Fragebogen wurde mitgeteilt, welches Ziel die Untersuchung habe, wie das Material eingesammelt wurde, wie es sortiert worden ist und auf welche Weise die Karte zustande kam. Antwort kam von 305 der 364 Distrikte, also von 85 %. Unter den 59 Distrikten, von denen keine Angaben kamen, befanden sich 26 Städte mit grösserer Bevölkerungszahl. Dorthin hatte ich das Frageformular nicht versandt, weil in diesen Städten aller Voraussicht nach mehrere Ärzte praktizieren und deshalb die Angaben der Provinzärzte von keiner grösseren Bedeutung sein konnten. Deshalb kann man sagen, dass nahezu von allen Provinzärztebezirken auf dem Lande Antwort einging (90 %).

Aus den Antworten ging hervor, dass in 95 % der Fälle die Provinzärzte die als multiple Sklerose erkannten oder verdächtigen Fälle an Krankenhäuser überwiesen, um die Diagnose verifiziert zu erhalten. Nur 11 Provinzärzte geben an, dass sie ihre Patienten zuhause behandelten, ohne dass diese irgendein-

mal im Krankenhaus aufgenommen gewesen wären zum Zweck der Verifikation der Diagnose.

Ausserdem geht aus den Antworten hervor, dass schätzungsweise 130—150 Fälle von multipler Sklerose oder im Verdacht solcher stehende von den Provinzärzten ins Krankenhaus überwiesen werden. Das stimmt mit der Anzahl Fälle, die ich erhalten habe recht gut überein. Während der von mir untersuchten zehnjährigen Zeitspanne wurden 1306 Fälle von multipler Sklerose herangezogen. Teilt man diese Zahl durch 10 so erhält man eine Jahresziffer von 130 Fällen. Es ist zu merken, dass die Angaben der meisten Provinzärzte oft die Verhältnisse eines Zeitraums von 10—20 Jahren umspannen.

Schliesslich geht aus den Antworten hervor, dass in 55 % (in 168) Fällen die Provinzialärzte die in der Karte vermerkte Frequenz der Krankheit für wahrscheinlich innerhalb ihres entsprechenden Bezirkes halten, dass sie ihnen in 14 % der Fälle zu hoch erscheint. In 6 % haben sie ein Fragezeichen hinsichtlich der Frequenz gemacht und in 22 % auf die Frequenzfrage nicht geantwortet. Es erscheint verständlich, dass so viele vor der Frage der Frequenz Zweifel hatten. Einer der bestimmendsten Gründe hierfür dürfte darin zu erblicken sein, dass die betreffenden Provinzärzte nur kurze Zeit ihren Dienst innerhalb dieses Distriktes versahen oder versehen hatten und daher nur über eine Erfahrung von einem oder einigen Jahren in demselben verfügten.

Die Fälle, in denen die Frequenz höher war, als die von den betreffenden Provinzärzten gemeinte, bedürfen keiner ausführlicheren Besprechung. Ein ganzer Teil der Patienten können natürlich unmittelbar das Krankenhaus aufsuchen und so den betreffenden Ärzten entgehen.

Nur in 3 %, d. h. in 9 Fällen wurde die von mir angegebene Frequenz als zu niedrig angesehen. Die hier gemachten Einwände sind folgende:

Drei der Distrikte gehören zum Bezirk Gävleborg:

Der Provinzarzt des Arbrå Distriktes gibt an, dass alle Fälle von multipler Sklerose in's Krankenhaus überführt werden. Allerdings gibt er nicht an wieviele er auf solche Weise jährlich in's Krankenhaus ein-

weist, aber sagt 1—2 alte Fälle innerhalb des Distriktes zu behandeln.

Der Provinzarzt des Bergsjö Distriktes gibt an, dass alle Patienten mit multipler Sklerose in's Krankenhaus überführt werden und dass auf diese Weise 1—2 neue Fälle jährlich eingesandt werden. Nach seiner Kenntnis sollen sich innerhalb des Distriktes ungefähr 8 alte Fälle befinden. Nach einer Revision der Lokalisation der Patienten, die vorgenommen wurde, nachdem die den Provinzärzten zugesandte Karte gezeichnet worden war, und die auf einer besseren Kenntnis des Wohnortes der Patienten zur Zeit ihrer zufälligen Erkrankung beruhte, wurden mehrere Patienten diesem Distrikt zugeführt, so dass er nun in eine höhere Frequenzziffer aufgestiegen ist.

Für den Distrikt Storvik wird mitgeteilt, dass alle Patienten in's Krankenhaus gesandt werden und dass deren Anzahl etwa 1 Fall jährlich ausmachen dürfte. Auch hier wurden bei der Revision einige weitere Fälle zugeführt, so dass die Frequenzziffer jetzt höher liegt.

In Östervåla im Bezirk Västmanland gibt der Provinzialarzt eine höhere Frequenz an. Bei der Revision des Materials konnten noch einige Fälle diesem Bezirk zugeführt werden, weshalb die Frequenz nun höher ist.

Zwei der Distrikte gehören zum Regierungsbezirk Värmland:

Im Molkom Distrikt konnte bei der Revision der Lokalisation der Fälle eine Steigerung der Frequenz in die nächsthöhere Ordnung vorgenommen werden.

Für den Distrikt Skönnerud teilt der Provinzarzt mit, dass er in 16 Jahren 3 Fälle gesehen habe. Berücksichtigt man die Einwohnerzahl von 6500 so will es mir scheinen, dass die angegebene Frequenz ziemlich genau der von mir festgestellten entspricht.

Auch im Distrikt Mariestadt im Reg. Bezirk Skaraborg sollte die Frequenz zu niedrig sein. Hier schickt der Provinzarzt die Patienten nicht in's Krankenhaus, sondern behandelt sie zuhause und will 6 Fälle in 5 Jahren gehabt haben. Ich muss hierzu darauf hinweisen, dass die Karte, die versandt wurde, keine anderen Angaben als diejenigen über die Frequenz auf dem Lande enthielt. Was die Stadt Mariestadt angeht, so kommt sie sowieso in eine höhere Frequenz als die vorher für die Umgebung angegebene. Aber auch diese konnte, nachdem bei der Revision ein Teil Fälle zugeführt werden konnten, erhöht werden.

Im Julita Distrikt des Reg. Bezirkes Södermanland wird ein Fall jedes dritte Jahr in's Krankenhaus gesandt und der Provinzialarzt behandelt alles in allem 5 Fälle von multipler Sklerose. Der Distrikt umfasst ca. 8000 Personen, werden 3 Fälle auf 10 Jahre gerechnet so erreicht die Frequenz nahezu die angegebene.

Für den Distrikt Eringsboda im Reg. Bezirk Blekinge teilt der Provinzialarzt mit, dass er alle Patienten in's Krankenhaus sendet und zwar jährlich ungefähr einen Fall. Auch hier hat eine Revision Fälle zugeführt, so dass die Frequenz erhöht werden konnte.

In 6 dieser 9 Distrikte hat also auf Grund einer Revision eine Erhöhung Platz greifen können, so dass diese Gebiete nun mit den von den Provinzialärzten gemachten Angaben besser übereinstimmen. Ich möchte hierbei darauf hinweisen, dass die Revision nicht erfolgte auf Grund der Antworten der Provinzialärzte, sondern darauf beruhte, dass die zeitraubende Korrespondenz mit den Patienten, Pastoren und Meldeämtern erst in letzter Zeit abgeschlossen werden konnte. Die übrigen Distrikte haben so gut wie alle neuentdeckten Fälle ins Krankenhaus gesandt. Dass trotzdem die Frequenz nachher nicht die gleiche beim Krankenhausmaterial wurde, mag darauf beruhen, dass ein Teil der überwiesenen Materials keine multiple Sklerose war. Es kann aber auch seine Ursache darin haben, dass die Fälle nicht mehr dahin lokalisiert wurden, wo sie entdeckt worden waren, denn die Möglichkeit, dass sie innerhalb eines anderen Distriktes lange vorher erkrankt waren, besteht ja.

Es will mir scheinen als ob also diese Umfrage eine recht gute Stütze für die Richtigkeit, der von mir gezeichneten Karten, gebracht hätte.

Der Mängel meiner Untersuchung bin ich mir durchaus bewusst. Die Fehlerquellen bei der Einsammlung des Materials, bei seiner Beurteilung, schliesslich bei der Lokalisation der Patienten sind sicher bedeutende gewesen.

*Dennoch scheint es mir, dass die Untersuchung ergeben hat, dass die multiple Sklerose wahrscheinlich eine gewisse aber nicht sehr markierte geographische Verbreitung hat, dass sie also zahlreicher innerhalb gewisser Bezirke auftritt, weniger zahlreich innerhalb anderer und dass diese Frequenzungleichheiten und Verschiedenheiten sich nicht allein aus reinen Zufälligkeiten erklären lassen.*

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## 4. Kapitel.

### *Das Vorkommen der multiplen Sklerose im Verhältnis zu demjenigen anderer Krankheiten.*

Die Fehlerquellen beim Zustandekommen der von mir gezeichneten Karte über das Vorkommen der multiplen Sklerose sind, wie ich bereits mehrfach ausführte, vielfache und trotzdem wird man zur Zeit eine sicherere Karte nicht erhalten können. Nach wie vor wird die Diagnosestellung schwer sein. Viele Fälle werden längerer Zeit unter anderer Diagnose behandelt werden. Die Bestimmung des Krankheitsanfangs wird oft schwierig sein. Möglicherweise würde man zu einem besseren Ergebnis gelangen, wenn jeder Patient, der jemals in irgend einem Krankenhaus behandelt wird, aufgesucht und eingehend untersucht würde. Ein Unternehmen, das im Hinblick auf die Menge der zu Untersuchenden und auf die dazu notwendige Zeit kaum durchführbar erscheint. So wird man sich also bis auf weiteres, wenn man sich einem Überblick über das Vorkommen der Krankheit im Lande verschaffen will, mit den Methoden begnügen müssen, die ich angewandt habe, und lediglich die Ergebnisse dieser Untersuchungen mit einer gewissen Reservation ausdeuten.

Unter Zugrundelegung der von mir gefertigten Karte habe ich versucht, das Vorkommen der multiplen Sklerose auch im Verhältnis zu anderen Krankheiten und mit Rücksicht auf einige in der Litteratur bereits früher diskutierte ätiologische Faktoren genauer zu erforschen. Hierfür bin ich genötigt, hauptsächlich vergleichende Kartenstudien durchzuführen, weil nach meiner Auffassung die Bearbeitung des verschiedenen statistischen Materials in seinem Verhältnis zueinander infolge der verschiedenen Beschaffenheit dieses Materials nicht angängig ist. Ausserdem erscheint mir eine derartige rein statistische Behandlung auch deshalb nicht geeignet, weil das Material aller

dieser Untersuchungen mit einer gewissen Reserve aufgenommen werden muss. Ich glaube demgegenüber, dass man sich möglicherweise ein recht gutes Bild darüber, wie die Dinge liegen, verschaffen kann, wenn man lediglich verschiedene Karten vergleichend durchforscht.

Das Vorkommen der multiplen Sklerose in ihrem Verhältnis zu anderen Krankheiten ist bisher nur wenig erforscht, was wohl hauptsächlich darauf zurückzuführen ist, dass sich auf dem Gebiet der geographischen Pathologie bisher überhaupt verhältnismässig wenige Untersuchungen vorfinden.

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### *Chorea minor, Struma endemica, Thyreotoxikosis.*

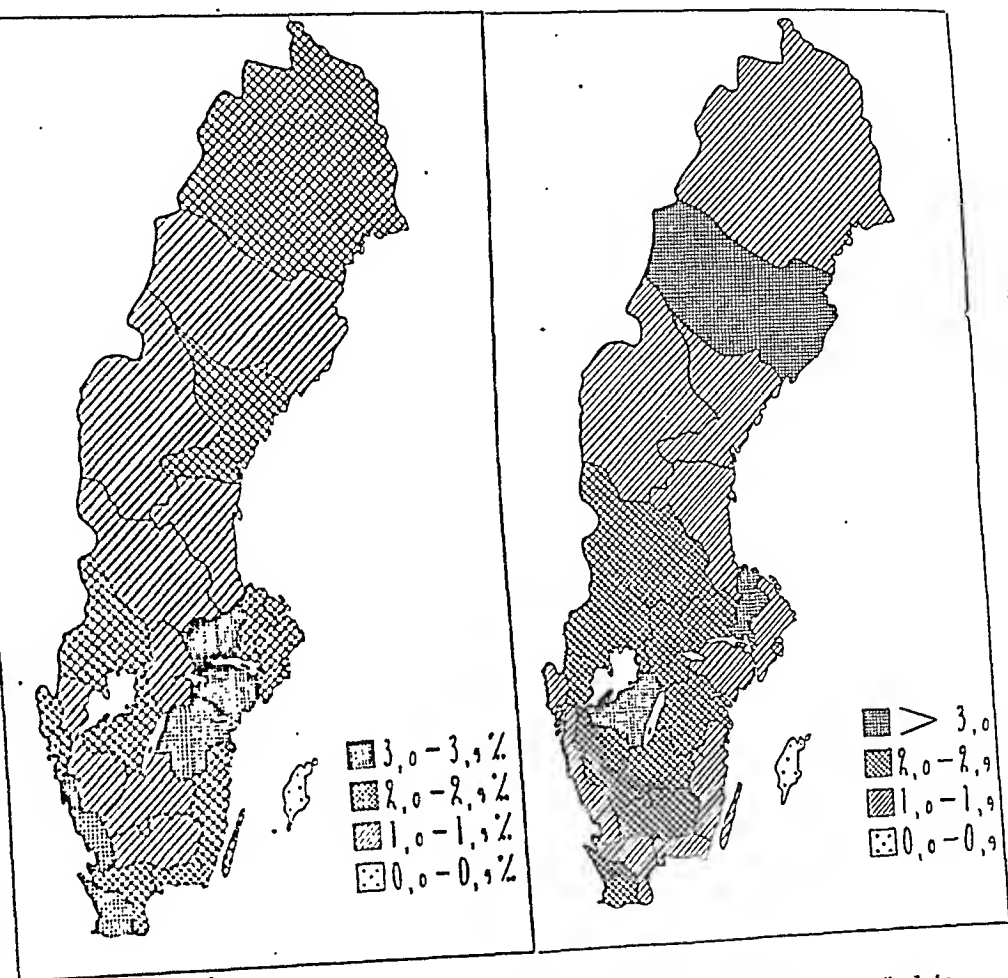
Davenport fand, dass diejenigen Krankheiten, die fast die gleiche Ausbreitung wie die multiple Sklerose innerhalb der USA. hatten, Chorea minor, Struma und Thyreotoxikose wären.

Was die Chorea angeht, so ist deren Frequenz sehr viel höher als die der multiplen Sklerose und sie tritt auch reichlicher als diese in verschiedenen Teilen der USA. auf. Dagegen haben beide Krankheiten das gemeinsame, dass sie selten in Ohio gefunden werden.

Eine Untersuchung über die Verbreitung der Chorea in Schweden gibt es nicht. Vor einigen Jahren habe ich das Vorkommen der akuten Polyarthrititis innerhalb des Landes während der gleichen Zeitspanne untersucht, die ich der vorliegenden Arbeit über das Vorkommen der multiplen Sklerose zugrunde legte, und eine allerdings nur auf die Berichte an die Kgl. Medizinalverwaltung gegründete Karte über die Ausbreitung der Polythrititis angefertigt. Ausserdem habe ich ihre Frequenz für die verschiedenen Regierungsbezirke angegeben. Wie bekannt besteht ein näherer Zusammenhang zwischen Chorea und akuter Polyarthrititis und es dürfte daher von Interesse sein, das Vorkommen der multiplen Sklerose und das der Polyarthrititis in Vergleich zu setzen. In figur 12 haben wir die Karte über das Auftreten der Polyarthrititis und in der Figur daneben das regierungshezirksmässige der multiplen Sklerose. Es hat den

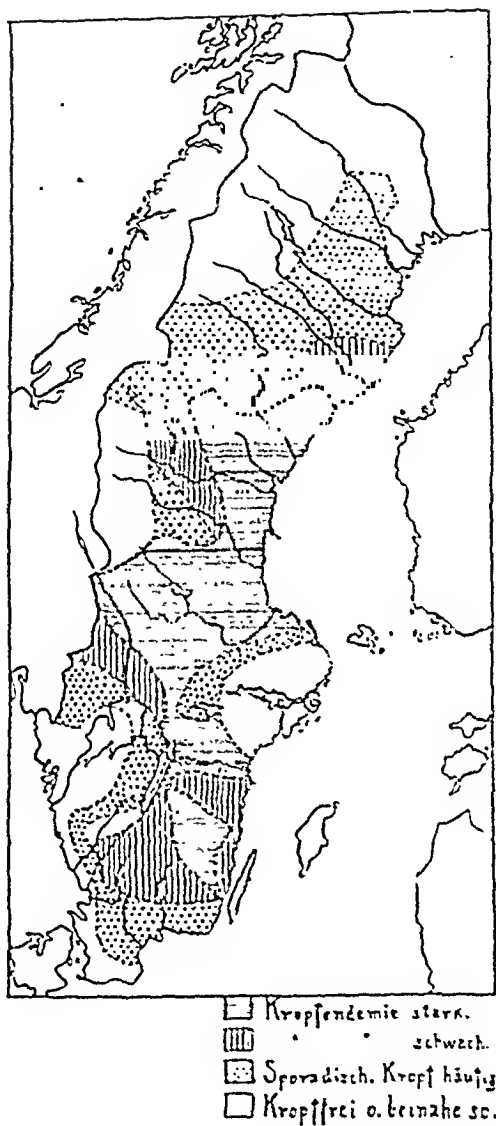
Anschein, als ob es eine irgendwie geartete absolute Übereinstimmung zwischen den beiden Krankheiten nicht gibt.

*Davenport* und auch *Steiner* betonen das parallele Vorkom-

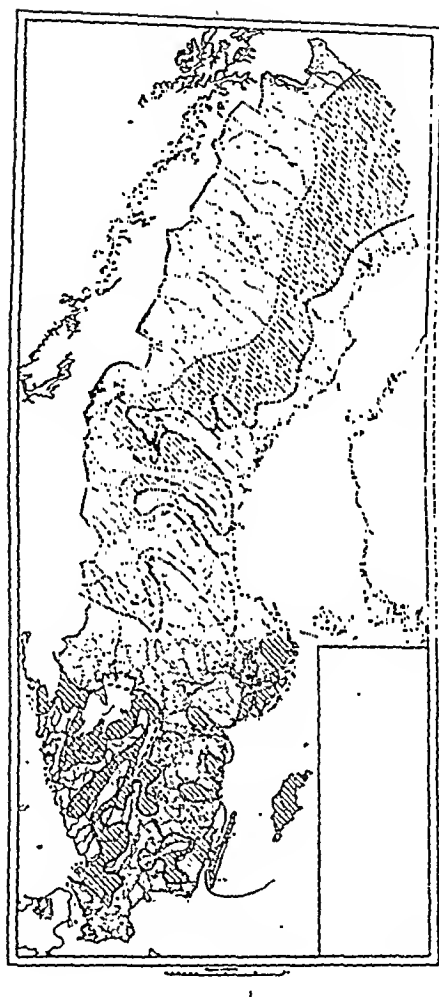


Figur 12. Auf die Berichte an die Kgl. Medizinalverwaltung gegründete Vorkommenskarte der Polyarthritis in Schweden (links). Die Frequenz ist für verschiedene Regierungsbezirke angegeben. In der Figur daneben (rechts) das regierungsmässige Vorkommen der multiplen Sklerose.

men von multipler Sklerose und Struma. *Steiner* behauptet zudem wahrgenommen zu haben, dass dies auch in gewissen Gebieten Deutschlands, besonders innerhalb Württembergs und Badens der Fall wäre. In anderen Teilen Deutschlands scheint



Figur 13. Gebiete mit verschiedener Kropffrequenz. Übersichtliche Kropfkarte von Schweden (nach A. Höjer: Kropfstudien, *Acta societatis medicorum suecanae*, 1931).



Figur 14. Generalisierte Vorkommenskarte der Thyreotoxiose in Schweden (nach T. Sällström: Vorkommen und Verbreitung der Thyreotoxiose in Schweden, Stockholm, 1935).

sie jedoch mit Struma nicht parallel zu laufen. In Schweden wurde die Strumaausbreitung von *A. Höjer* erforscht. Seine Karte ist in der Figur 13 wiedergegeben. Auf die näheren Umstände ihrer Entstehung kann ich hier nicht eingehen, sondern stelle sie nur zum Vergleich mit meiner Karte der Verbreitung der multiplen Sklerose. Es findet sich keine auffällige oder durchgängliche Übereinstimmung.

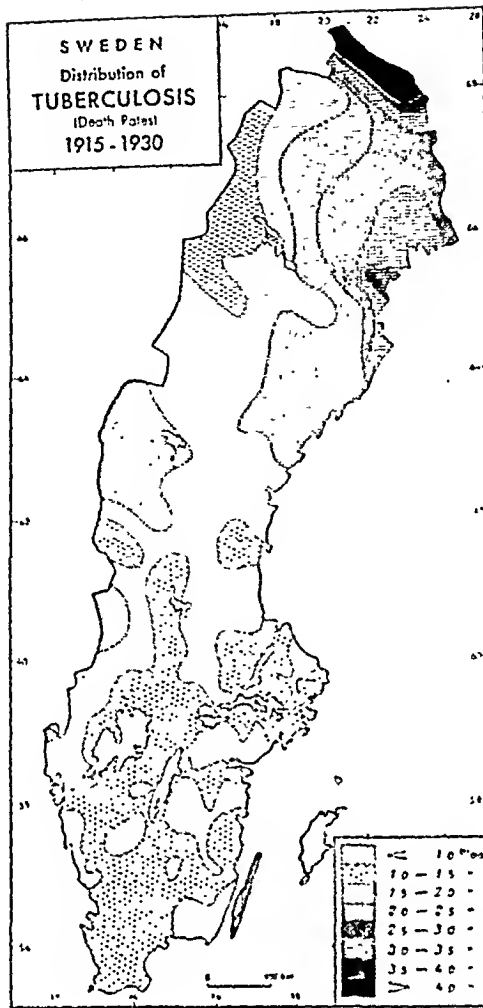
*W. Peterson* meint, dass die multiple Sklerose in den USA. ziemlich tren der Verteilung der Thyreotoxikose folgt. Nach *Steiner* soll dies eine Folge davon sein, dass die Ausbreitung der Thyreotoxikose recht nahe derjenigen der gewöhnlichen Struma folgt. Indessen hält *Steiner* die Parallelität des Vorkommens der multiplen Sklerose auf der einen und der Struma und Thyreotoxikose auf der anderen Seite nicht für zufriedenstellend bewiesen. Hierzu möchte ich darauf hinweisen, dass irgendwelches absolutes Übereinstimmen zwischen dem Vorkommen der einfachen Struma und der Thyreotoxikose in Schweden von mir nicht gefunden werden konnte. Die von mir erhaltene generalisierende Karte für die Ausbreitung der Thyreotoxikose innerhalb Schwedens findet sich in Figur 14. Sie wurde auf dieselbe Weise wie diejenige über die multiple Sklerose ermittelt und dürfte mit dieser keine irgendwie sichere Übereinstimmung zeigen.

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### *Tuberkulose.*

Dass ein ätiologischer Zusammenhang zwischen multipler Sklerose und Tuberkulose bestehen soll, ist ziemlich lebhaft diskutiert worden. Grosses Interesse erweckten, wie ich bereits anführte, *Löwenstein* und *Marburg*, als es ihnen zusammen glückte Tuberkelbacillen im Blute eines an multipler Sklerose Erkrankten nachzuweisen. Später hat man dann allerdings im Blute der verschiedensten Nerven- und Geisteskrankheiten Tuberkelbacillen nachweisen können und die Theorie der Tuberkulose als ätiologische Ursache der multiplen Sklerose hat deshalb durch spätere Untersuchungen nicht bekräftigt werden

können. Allerdings hat danach *Ahringsmann* den Gedanken aufgenommen und als seine Theorie vorgelegt, dass die multiple Sklerose eine Form der Metatuberkulose sein sollte, in Analogie mit den metasymphilitischen Veränderungen bei Lues. Aber er hat niemals Tuberkelbacillen in den mikroskopischen Schnitten der Herde der multiplen Sklerose nachweisen können. Trotzdem sieht er darin keinen Gegenbeweis und weist vielmehr daraufhin, wieviel Zeit es gekostet hatten, ehe die metasymphilitischen Veränderungen als syphilitische erkannt wurden, und die lange es dauerte ehe die Wassermannsche Reaktion zustande kam. Als Stütze seiner Auffassung weist *Ahringsmann* darauf hin, dass die multiple Sklerose ohne Zweifel in neuerer Zeit häufiger geworden sei, und er erinnert daran, dass die Tuberkulosemortalität ganz enorm während des vorigen Krieges und während der Inflationsperiode in Deutschland zunahm. Mit einem Zwischenintervall von 8—10 Jahren soll man nach 1925—1930 erhöhte Fälle von multipler Sklerose erhalten, was auch geschah. In Figur 15 ist eine Karte der Tuberkulosemortalität für die Jahre 1915—1930 wiedergegeben, die *Uddströmer* auf die gleiche Weise ermittelte, wie die meinige der multiplen Sklerose ermittelte wurde, also auch hier wurde nicht so sehr Rücksicht auf die administrativen Bezirke genommen, sondern mehr auf das wirkliche Vorkommen der Krankheit. Vergleicht man diese Karte mit meiner generalisierenden Karte über die multiple Sklerose findet man keinerlei Übereinstimmung, auch keine absoluten gegensätzlichen Verhältnisse. Sicherlich hat die Tuberkulose in Schweden nicht immer gerade diese Ausbreitung gehabt, sondern die höhere Frequenz ist, wie bekannt, so nach und nach von Süden nach Norden fortgeschritten. Dennoch glaube ich nicht — auch wenn man sich die multiple Sklerose als metatuberkulöse Manifestation denkt —, dass dieses Fortschreiten von irgendwelcher Bedeutung sein sollte, weil es zeitlich sehr viel länger zurückliegt, als die eventuelle tuberkulöse Infektion bei Patienten mit multipler Sklerose ausmacht. In einem früheren Kapitel habe ich bereits die Frage der Tuberkulose bei multipler Sklerose und in den Familien dieser Kranken behandelt und bin zu dem Ergebnis gekommen, dass irgendwelche erhöhte Heredität oder Belastung mit Tuberkulose bei



Figur 15. Die Verbreitung der Tuberkulose in Schweden (Mortalitätszahlen 1915—1930) (nach M. Uddströmer: The occurrence of lymphogranulomatosis in Sweden, *Acta tuberculosa scand. suppl. I. 1934*).

den Patienten mit multipler Sklerose nicht vorgefunden wird, auch keine erhöhte Geneigtheit selber an Tuberkulose zu erkranken. Wie ich vorher darlegte war die Frequenz der multiplen Sklerose keinen auffallenden Veränderungen während der Untersuchungszeit unterworfen, während dagegen die Mortalität für Tuberkulose ständig sinkende Ziffern zeigte. Irgendein Zusammenhang zwischen Tuberkulose und multipler Sklerose kam also bei dieser Untersuchung nicht vor.



Die Theorie, dass die multiple Sklerose von einer Spirochaete verursacht werden sollte, hat sich grossen Interesses erfreut. *Kuhn* und *Steiner* glückte es zuerst spirochaetengleiche Bildungen im Nervensystem bei multipler Sklerose aufzuweisen, danach haben dann mehrere Forscher diese Frage diskutiert. Es gelang Mehreren diese sogenannten Spirochaeten aufzuweisen. Unter anderen *Hassin*, *Diamond*, *Scheinker*, *Schuster*, *Siemering* und *Wilson*. *Wilson* stellte die Theorie auf, dass die Spirochaeten durch Ratten auf den Menschen übertragen würden in Analogie zu den Verhältnissen bei der Morbus Weil. Diese Hypothese sollte nach ihm die Tatsache erklären, warum die multiple Sklerose so häufig in der Umgebung der grossen Seen in den USA. wäre und in den Sumpfbereichen um Peterborough in England. Er kann aber keinen positiven Beweis für die Richtigkeit seiner Theorie erbringen. Die überwiegende Mehrzahl der Forscher betrachtet diese Spirochaetentheorie auch mit einem gewissen Misstrauen.

Da man sich eine gleichgeartete Verbreitungsweise für multiple Sklerose und Morbus Weil gedacht hat, wäre natürlich eine vergleichende Studie der geographischen Pathologie beider Krankheiten aus verschiedensten Gesichtspunkten von Interesse. Ausserdem ist die Morbus Weil erst kürzlich in Schweden von *Malmgren* erforscht worden.

Hauptsächlich sind es wohl zwei Punkte, die sich für eine Diskussion eignen könnten, nämlich die Berufsverhältnisse und die Verbreitung. *Malmgren* findet in seinem Material, dass Morbus Weil am meisten bei Land- und Stallarbeiten angetroffen wird. Um 50 % seiner Patienten gehören dieser Berufsgruppe an. Betrachten wir mein Material so haben wir auch dort ungefähr 50 % der Patienten mit Landwirtschaft und den dazugehörenden Berufszweigen beschäftigt, aber dies ist, wie ich nachweisen konnte, ungefähr normale Relation der Berufsgruppen innerhalb des Landes. Das was in *Malmgrens* Arbeit möglicherweise dafür sprechen kann, dass das Übergewicht innerhalb der genannten Berufe in seinem Material sicher ist, ist die Tatsache, dass darin Männer nahezu 3 mal so zahlreich sind wie

Frauen. In meinem Material überwiegen dagegen die Frauen etwas. Die nächste grössere Gruppe von Patienten in *Malmgrens* Material sind die Schlächtereiarbeiter. Irgenwelche Übergewicht für diese findet sich in meinem Material nicht. Die Berufsverhältnisse bei den beiden Krankheiten zeigen also keine grössere Übereinstimmung.

Was die Ausbreitung angeht, so kann man sowohl Gleichheiten wie Ungleichheiten feststellen, auch Gegensätze finden sich. Gleichheiten bestehen darin, dass sich zahlreiche Fälle von Morbus Weil in den Regierungsbezirken Värmland, Örebro, Skaraborg, Älfsborg, Jönköping, Östergötland und Malmöhus finden, in denen auch die multiple Sklerose recht häufig vorkommt. Keine oder nur vereinzelte Fälle finden sich in den Regierungsbezirken Bohus, Halland, Blekinge, Kalmar und in gewissen Teilen von Stockholm. In diesen Bezirken ist auch die multiple Sklerose selten. Verschiedene Ausbreitung zeigen beide Krankheiten für die Regierungsbezirke Upsala, Västmanland, Kopparberg, und Västernorrland. Innerhalb dieser Bezirke ist Morbus Weil selten, während dagegen die multiple Sklerose ziemlich reichlich vorkommt. Sonach hat auch die Verbreitung beider Krankheiten keine durchgehende Gleichheit.

*Es will also scheinen, als ob irgend ein Zusammenhang zwischen der geographischen Pathologie der multiplen Sklerose und derjenigen der Morbus Weil nicht bestände. Da Morbus Weil im grossen hinsichtlich seiner Ausbreitung derjenigen der infizierten Ratten folgt, bedeutet dies auch, dass die multiple Sklerose wahrscheinlich in keinem Zusammenhang mit den Ratten steht, die morbus Weil übertragen.*

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### *Blei.*

Dass Blei für die Entstehung der multiplen Sklerose von Bedeutung sei, ist unter Anderen von *Cone* und Mitarbeitern vorgebracht worden, aber es sei selten sagt *Drobnes*, dem es nur bei zwei Patienten gelang Blei nachzuweisen.

Blei als ätiologischer Faktor kann natürlich nicht eingehender an einem Material, wie dem meinigen studiert werden. Auf Grund meiner Untersuchungen kann man lediglich in gewissem Umfang beurteilen, wieweit Patienten mit multipler Sklerose der Berührung mit Blei ausgesetzt waren. Blei kommt wohl hauptsächlich in Berufen wie Anstreicher, Maschinenarbeiter und Röhrenarbeiter, sowie in gewissen chemischen Industrien vor. Nur 18 meiner Patienten waren im Maler oder Anstreicherberuf beschäftigt, 19 waren in mechanischen Werkstätten tätig, 3 als Schmiede, 2 als Dachdecker bzw. Klempner, 9 als Elektriker, 4 als Röhrenarbeiter und 7 als Typographen. Sonach finden sich nicht die geringsten Prädominieren der multiplen Sklerose innerhalb irgendetwelcher Berufe, bei denen die Patienten der Beschäftigung mit Blei ausgesetzt sind.

*Irgendwelche Anhaltspunkte dafür, dass Blei von einer ätiologischen Bedeutung bei der multiplen Sklerose wäre, können sonach aus dieser Untersuchung nicht hergeleitet werden.*

Vielleicht hat Blei irgendeine andere Bedeutung auf die multiple Sklerose, als gerade ätiologische.

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### *Die Zeckentheorie.*

Steiner hat die Theorie aufgestellt, dass die multiple Sklerose unter den Menschen durch den Biss von Zecken verbreitet werden soll. Unter den Zeckentypen, die in Frage kommen sollen, steht *Ixodes ricinus* in vorderster Reihe. Ein Teil der Forscher sind in Steiners Fuss-spuren getreten, u. A. *Curschmann*. Es gelang ihnen nachzuweisen, dass eine grosse Zahl an multipler Sklerose Erkrankter früher von Zecken gebissen worden waren. Steiner gibt selbst an, dass er bei 50 % aller von ihm untersuchter Fälle von multipler Sklerose Reste von Zeckenbissen gefunden habe. *Marburg*, der seine Aufmerksamkeit speciell auf das Vorkommen von Zeckenbissen bei Patienten mit multipler Sklerose gerichtet hat, fand nur einmal auf mehrere Hundert Fälle von multipler Sklerose einen Zeckenbiss. Auch *Allison* hält die Zeckenbisse bei multipler Sklerose für ungewöhnlich. Ebenso

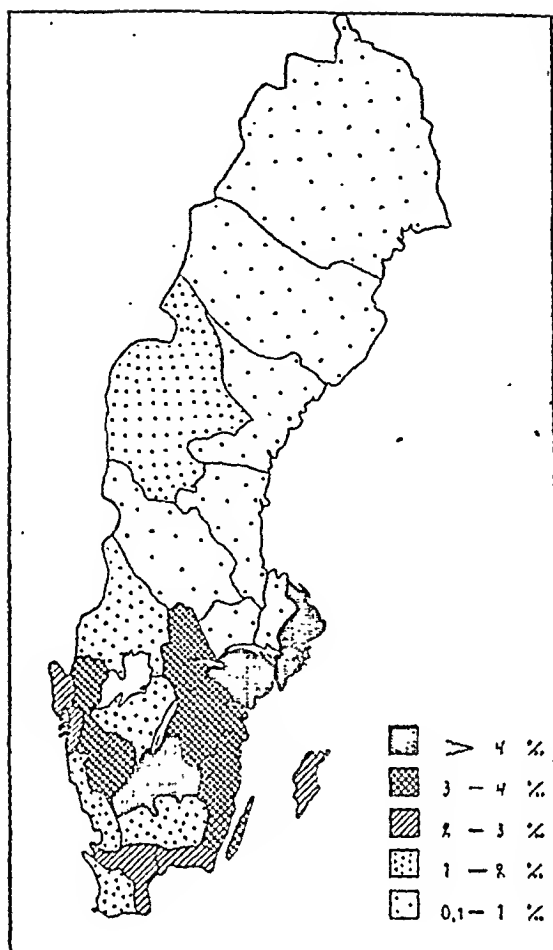
zweifelt *Bing* an der Bedeutung der Zecken bei der multiplen Sklerose und weist darauf hin, dass diese Tiere in Afrika und Australien eine Nervenkrankheit übertragen, die sich völlig von der multiplen Sklerose unterscheidet.

In meinem Material danach zu forschen, ob die Patienten Reste von Zeckenbisse gehabt, wäre nicht möglich gewesen. Es konnte auch keine Rede davon sein, dieses Detail in meinem Fragebogen zu erfragen, denn es erschien mir so gering und für die infrage kommenden Individuen so bedeutungslos, dass erschöpfende und sichere Antworten wahrscheinlich nicht zu erhalten gewesen wären.

Die Möglichkeiten, die sich zur Beurteilung der Zeckentheorie in meiner Arbeit bieten, sind nicht gross. Hauptsächlich dürften es zwei Punkte sein, die für eine Diskussion in Frage kommen, und zwar zunächst die Möglichkeit für die Patienten Zeckenbisse zu erhalten, etwas, das nahe mit dem Beruf und der Beschäftigung der Patienten zusammenhängt, und zum anderen die Ausbreitung der Krankheit in den Bezirken des Landes, in denen Zecken vorkommen.

Was den Beruf angeht, so müssen die Patienten, die denkbareweise Zeckenbissen ausgesetzt sein können, überwiegend ausserhause Arbeiter sein. Zecken kommen hierzulande hauptsächlich in wasserreichen Gehölzen und Wiesengründen vor, wo sich reichliche Vegetation von beispielsweise Hasel, Erle, Jungbirke, Espe und Weide findet. Derartige Gebiete sind nun für gewöhnlich Weidemark für Rinder, so dass in erster Linie die landbewirtschaftende Bevölkerung es sein müsste, die dem Erkrankten an multipler Sklerose ausgesetzt war. Wie aus dem Kapitel über die Berufsverteilung bei der multiplen Sklerose hervorgeht, sind um 50 % der Patienten in der Landwirtschaft, Fischerei und in der Industrie der Steine und Erden, den Berufen, die wohl am ehesten in dieser Richtung in Betracht kommen, tätig. Aber das bedeutet noch kein proportionales Übergewicht dieser Berufsgruppen. Natürlich ist es auch denkbar, dass Patienten innerhalb anderer Berufsgruppen bei mehr zufälligem Aufenthalt auf dem Lande von Zecken gebissen wurden. Die Berufsverteilung gibt infolgedessen keine direkte Stütze für die Zeckentheorie.

Die Verbreitung der Zecken in Schweden ist nicht sehr erforscht. Eine Übersicht über schwedische Zecken wurde von *Schulze* 1930 überreicht. Dagegen ist es nach einer persönlichen Mitteilung von Professor T. *Gislén*, Lund, ausgeschlossen aus den hier im Lande gemachtem Streufunden von Zecken oder aus Beobachtungen über deren Nichtvorhandensein irgendwelche Schlüsse über deren wirkliches Vorkommen zu ziehen. Die gewöhnlichste Zecke hierzulande ist *Ixodes ricinus*, gerade der Typ, der im Verdacht steht die Krankheit zu verbreiten. Aber es findet sich keine Untersuchung, die ausführlicher die Ausbreitung in Schweden behandelt. Daher kann eine vergleichende Gegenüberstellung des Vorkommens der multiplen Sklerose und der Ausbreitung der Zecken zufriedenstellend nicht vorgenommen werden. Und doch findet sich eine Möglichkeit, sich ein Bild darüber zu verschaffen, wo diese Tiere hansen. Es ist eine alt bekannte Sache, dass eine Rinderkrankheit, sogenannte Piropiasmose (Blutstallung) von Mikroorganismen hervorgerufen wird (*Piroplasma bovis*), die durch Zeckenbiss auf die Tiere übertragen werden. Piropiasmen gibt es an Stellen, wo Zecken fehlen, nicht, dagegen kann sie fehlen an Stellen, wo sich Zecken finden, denn zur Übertragung der Krankheit ist ja notwendig, dass sie mit den obenzeichneten Mikroorganismen infiziert sind. Durch das Studium der Verbreitung der Piropiasmose kann man eine gewisse Vorstellung über das Vorkommen der Zecken im Lande bekommen. *Klarin* hat die Piropiasmose in Schweden während der Jahre 1913—1919 erforscht. Auf der Grundlage der von ihm für die Verbreitung der Krankheit innerhalb des Landes aufgestellten Frequenztablelle habe ich die Karte der Figur 16 zusammengestellt, wo die Frequenz in Promille kranker Tiere angegeben ist. Zusammengekommen waren während der Untersuchungsperiode über 41 Tausend Tiere angemeldet worden. Wenn wir diese Karte der Verbreitung der Piropiasmose mit derjenigen des Vorkommens der multiplen Sklerose vergleichen, so finden sich nur wenige Gemeinsamkeiten. Reichlicheres Vorkommen von multipler Sklerose und Piropiasmose ergibt sich in den Regierungsbezirken Östergötland, Jönköping, Älvsborg, sowie Örebro. Entgegengesetzte Verhältnisse zeigen die beiden Krankheiten in unter anderen den



Figur 16. Das Vorkommen der Piroplasmosis in Schweden. Die Karte ist konstruiert nach Zifferangaben aus einer Arbeit von E. Klarin (Klarin: *Blodställning hos nötkreatur*, Skand. Kreatursförsäkr.AB. Årsberättelse 1925, Stockholm).

Regierungsbezirken Upsala, Stockholm, Kalmar, Västmanland, Kopparberg und Värmland. Eine Detailübereinstimmung findet sich also nicht zwischen den beiden Frequenzkarten. Man muss sich aber immer vor Augen halten, dass eine Karte über das Vorkommen der Piroplasmose im Lande keine solche der Ausbreitung der Zecken darstellt, sondern nur Plätze aufzeigt, an denen infizierte Zecken vorkommen.

Die Voraussetzungen für die Beurteilung der Frage über die Bedeutung der Zecken für die multiple Sklerose sind also in

meinem Material nicht so günstig. Es wäre ja möglich gewesen, dass, wenn es irgendeine genaue Frequenzstudie über das Vorkommen der Zecken im Lande gegeben hätte, man auf Grund dieser zu gewissen Schlüssen über die Bedeutung der Zecken bei der multiplen Sklerose gekommen wäre, denn wenn diese irgend eine Bedeutung haben sollten, so müsste ja das Vorkommen der multiplen Sklerose in die Verbreitungsgebiete der Zecken fallen. Zunächst muss die Frage offen gelassen werden, bis bessere Voraussetzungen für ihre Beurteilung gegeben sind. Möglicherweise kann man das vorliegende Material von multipler Sklerose zugrunde einer Spezialuntersuchung liegen, die gewisse kleinere, auf die Frequenzkarte gestützte Gebieten umfassen. Eine detaillierte Studie über die Zeckentheorie wurde hier in Schweden vor einigen Jahren von Doktor R. Almkvist begonnen. Es ist zu wünschen, dass hier eine Mitarbeit zustande kommen könnte, und dass man auch Biologen, die das Zeckenvorkommen im Lande studiert haben, über diese Probleme interessieren könnte.

*Die Untersuchung ist nicht geeignet die Frage über die Bedeutung der Zecken in der Ätiologie der multiplen Sklerose zu beantworten. Die Ausbreitung und das Vorkommen der Zecken in Schweden ist nicht erschöpfend erforscht. Irgendein Zusammenhang zwischen Piroplasmose bei Rindern — einer Krankheit, die durch Zecken übertragen wird — und multipler Sklerose hat nicht nachgewiesen werden können.*

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## 5. Kapitel.

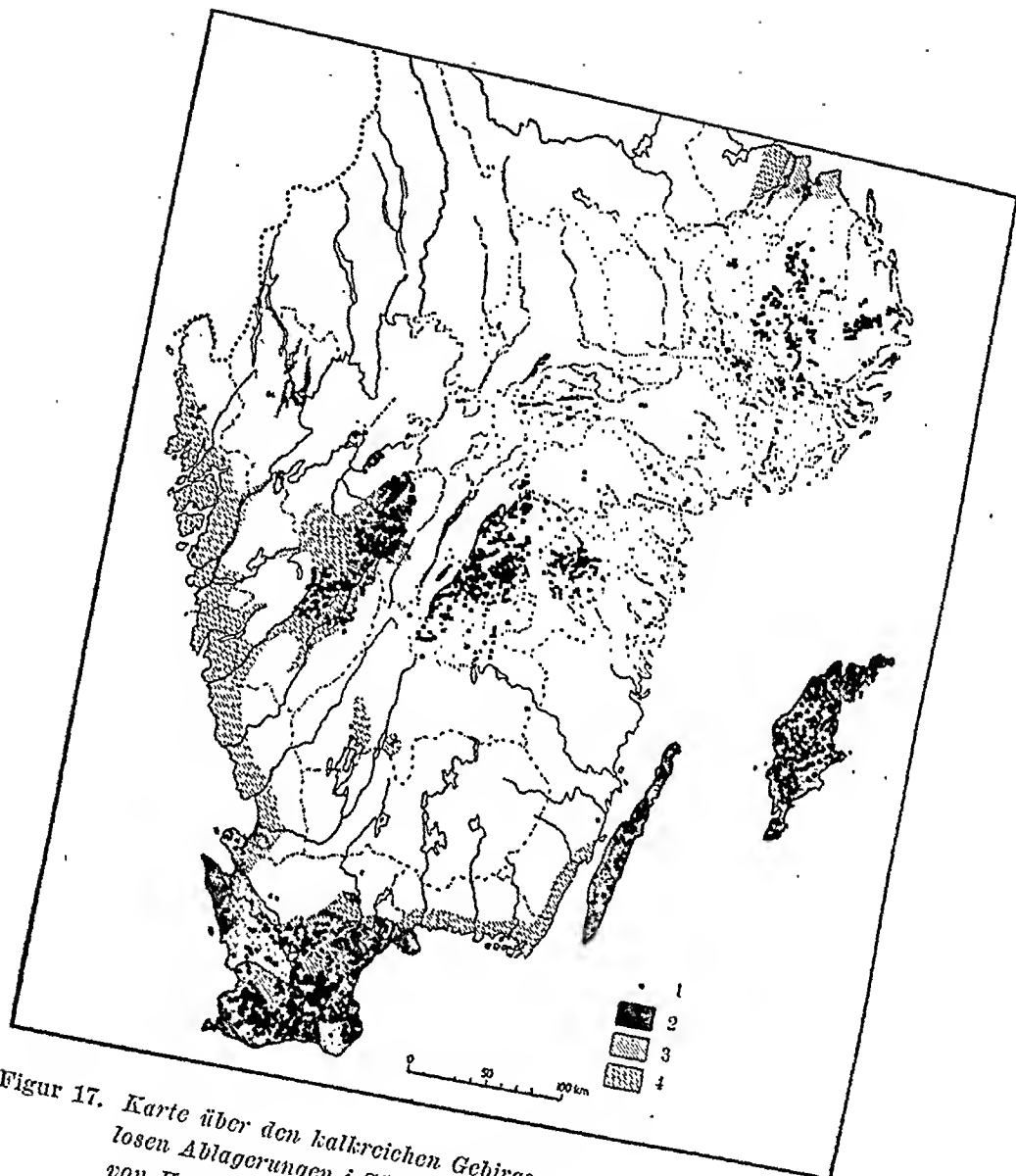
### *Das Vorkommen der multiplen Sklerose und ihr Verhältnis zu verschiedenen geographischen Faktoren.*

Die Karte über das Vorkommen der multiplen Sklerose war nicht der Ausgangspunkt einer eingehenderen naturgeographischen Studie. Eigentlich sind es nur zwei verschiedene Gesichtspunkte, die in gewissem Mass beachtet worden sind, nämlich das Verhältnis der Krankheitsfrequenz zur Ausbreitung des Ackerareals innerhalb des Landes und das Vorkommen von Kalk.

Unzweifelhaft findet sich eine gewisse Übereinstimmung zwischen dem Vorkommen der multiplen Sklerose und der Ausbreitung des Ackerareals innerhalb des Landes. Reichlicheres Vorkommen der multiplen Sklerose wird in den grossen Landwirtschaftsdistrikten in den Regierungsbezirken Upland, Västmanland, Örebro, Östergötland, Västergötland, Värmland und Malmöhus gefunden. Dagegen ist die multiple Sklerose nicht so gewöhnlich in den Landwirtschaftsdistrikten in Södermanland, Blekinge, sowie an der Westküste, während sie häufiger in den Regierungsbezirken Kronoberg und Jönköping ist, von denen nicht gerade behauptet werden kann, dass sie direkte Ackerbaubezirke wären. Eine auffälligere Übereinstimmung scheint indessen nicht gegeben zu sein.

Cone und seine Mitarbeiter haben bei ihren Untersuchungen über die Bedeutung des Bleis bei der multiplen Sklerose unter anderem eine Reihe von Umständen gefunden, die dafür sprechen, dass Kalk eine gewisse therapeutische Wirkung bei der multiplen Sklerose habe und zwar dergestalt, dass er die Progredienzen der Krankheitssymptome hemmen sollte und zugleich die Aussonderungen von Blei mindern würde. Wie das sich nun auch verhalten mag, jedenfalls mag es mit Beziehung hierzu von Interesse sein, zu sehen, wie die Ausbreitung der mul-





Figur 17. Karte über den kalkreichen Gebirgsgrund und die kalkreichen losen Ablagerungen i Süd- und Mittelschweden. 1. Vorkommnisse von Kalkgyttja, Seekalk und Kalktuff (bezeichnet einen hohen Kalkgehalt des Grundwassers). 2. Gebirgsgrund von Kalkstein. 3. Gebiet (ohne Gebirgsgrund von Kalkstein) mit umfassendem von kalkreichen ( $\text{CaCO}_3$ ) losen Ablagerungen (Eismerlon, auch jüngeren Tonen und bisweilen gröberen Bodenarten). 4. Gebiet ohne Gebirgsgrund von Kalkstein mit Vorkommen vom schwächeren Kalkgehalt ( $\text{CaCO}_3$ ) in den losen Ablagerungen (zumeist nur in den tieferen Schichten des Eismerlons). — Nach G. Lundquist in »Växternas liv», II, Stockholm 1934.

tiplen Sklerose sich zu dem Kalkvorkommen des Landes verhält. In Figur 17 findet sich eine Karte, die das Kalkvorkommen im südlichen und mittleren Teil Schwedens zeigt. Auf ihr findet man ein recht reichliches Vorkommen der multiplen Sklerose gerade innerhalb der kalkreichen Flachländer der Regierungsbezirke Öster- und Västergötland, Skåne und Uppland. Im Regierungsbezirk Värmland, wo es auch reichlich multiple Sklerose gibt, ist dagegen der Kalk in der Natur ungewöhnlich. Nach *Sjögren* gibt es lediglich in der Umgegend von Filipstad Kalk in Form von Urkalksteinsgrund, während im übrigen Bezirk Kalk sowohl als Urgrund, wie als lose Ablagerung fehlt. Es ergibt sich also keine Übereinstimmung zwischen den Gegenden mit Vorkommen von Kalk oder mit Fehlen von Kalk und denjenigen der multiplen Sklerose. Dass der Kalk von irgendwelcher Bedeutung für die Entwicklung der multiplen Sklerose sein sollte, erscheint von dieser Untersuchung aus zweifelhaft.

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## 6. Kapitel.

### *Das Ergebnis der Untersuchung.*

Über die multiple Sklerose in Schweden wurde eine geographisch-pathologische Studie durchgeführt, der Krankenhansmaterial der multiplen Sklerose aus allen Krankenhäusern innerhalb des Landes während einer 10 Jahresperiode von 1925 bis 1934 zu Grunde lag.

Das Material umfasst 1365 Fälle, bei denen die Diagnose — multiple Sklerose — auf Grund von Symptomen, die auf multiple Herde im Nervensystem zurückgeführt werden können, gestellt wurde und in engem Zusammenhang mit einer genauen Anamnese. Über den Charakter der verschiedenen Fälle, sowohl was die ausgebildete multiple Sklerose betrifft, wie auch über die praemonitorischen Symptome werden tabellarische Angaben gegeben. In 735 Fällen war die Diagnose der multiplen Sklerose unsicher oder fehlerhaft. Eine ausführliche Analyse dieser Fälle wird mitgeteilt.

Im Mittel hat die Anzahl der jährlichen Fällen von multipler Sklerose während der Jahre 1925—1934 136 Fälle betragen. Weder eine Erhöhung noch eine Verminderung der Frequenz ist während dieser Zeit wahrgenommen worden.

Bei nahezu 75 % der Fälle beginnt die multiple Sklerose im Alter zwischen 16 und 35 Jahren. Nur vereinzelte Individuen erkranken vor dem 10 ten Lebensjahr.

Die multiple Sklerose findet sich häufiger bei Frauen als bei Männern. Die Differenz ist nicht gross, aber nachweisbar. Sie kann nicht durch eine wechselnde Zusammensetzung der Bevölkerung innerhalb geographisch verschiedener Bezirke oder innerhalb verschiedener Altersgruppen erklärt werden.

Eine genaue Studie der Berufsverteilung bei den Patienten mit multipler Sklerose zeigt ein unbedeutendes Überwiegen der-

jenigen die in der Landwirtschaft, der Textilindustrie, dem Handel, den öffentlichen Diensten oder in den freien Berufen beschäftigt sind. Von Interesse ist es, zu sehen, dass die Eltern der Kranken im selben Umfang in der Landwirtschaft beschäftigt waren wie die multiple Sklerose innerhalb dieser Berufsgruppe auftritt.

Die Untersuchung hat gezeigt, dass die Krankheit innerhalb der Familien von Patienten, die an multipler Sklerose leiden, mehr als 80 mal so oft vorkommt, als in der Durchschnittsbevölkerung. Auch das Vorkommen von Geisteskrankheiten in den Familien der Patienten mit multipler Sklerose ist bedeutend grösser als bei der normalen Bevölkerung. Die ganze neuropsychogene Belastung erreicht eine Höhe von ungefähr 16 %.

Aus der Untersuchung geht hervor, dass sich bei den Patienten mit multipler Sklerose keine erhöhte familiäre Belastung mit Tuberkulose findet. Diese Patienten sind auch nicht in grösserem Masse selber der Gefahr ausgesetzt an klinisch manifestierbarer Tuberkulose zu erkranken.

Die Mortalität erreicht 25 %, was etwa 35 Personen jährlich entspricht.

Die Dauer der Krankheit wurde im Mittel mit 9 Jahren berechnet.

1306 Fälle konnten geographisch lokalisiert werden. Davon waren 392 in Städten 914 auf dem Lande ansässig. Das Verhältnis der in den Städten Ansässigen zu den auf dem Lande Ansässigen entspricht demjenigen der normalen Bevölkerung. Die Krankheit scheint in etwas höherem Ausmass die bodenständige Bevölkerung gegenüber der Zuziehenden zu treffen.

Die multiple Sklerose hat wahrscheinlich eine gewisse aber nicht sehr markierte geographische Ausbreitung. Sie kommt innerhalb gewisser Bezirke zahlreicher, weniger zahlreich in anderen Bezirken vor und diese Frequenzverschiedenheiten lassen sich nicht mit einfachen Zufällen erklären.

Ein Zusammenhang zwischen dem Vorkommen der multiplen Sklerose und der Ausbreitung der Tuberkulose oder einem Teil anderer Krankheiten ergab sich bei dieser Untersuchung nicht.

Irgendwelche Anhaltspunkte dafür, dass Blei eine ätiolo-

gische Ursache für die multiple Sklerose sei, sind nicht gefunden worden.

Die Untersuchung ist nicht geeignet, die Frage nach der Bedeutung der Zecken innerhalb der Ätiologie der multiplen Sklerose zu beantworten. Die Ausbreitung und das Vorkommen der Zecken innerhalb Schwedens ist nicht eingehend genug erforscht. Irgendein Zusammenhang zwischen der Piroplasmose bei Rindern — einer Krankheit, die durch Zecken übertragen wird — und multipler Sklerose hat auch nicht aufgezeigt werden können.

Eine ausführlichere naturgeographische Studie der Frequenzkarte der multiplen Sklerose ist nicht durchgeführt worden.

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Tabelle 20. Einwohnerzahl verschiedener Regierungsbezirke, ganze Anzahl der multiplen Sklerose und ihre Frequenzzahlen für die verschiedenen Bezirke. Die Frequenzzahlen drücken die Anzahl der multiplen Sklerose pro 10 000 Einwohner aus.

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort an-sässig.
STOCKHOLM	502.207	90	1,8	39
<i>Stockholms län:</i>				
Frösåkers härad	12.716	4	3,1	4
Närdinghundra härad	8.095	4	5,0	2
Väddö-Häverö härad	9.449	1	4,3	4
Bro-Vätö skeppslag	3.977	1	2,5	1
Lyhundra härad	4.447	2	4,5	2
Frötuna-Länna skeppsl.	7.176	1	1,4	1
Sjuhundra härad	4.934	0	0	0
Långhundra härad	4.833	3	6,3	3
Ärlinghundra härad	6.558	2	3,0	1
Seminghundra härad	3.863	0	0	0
Vallentuna härad	6.413	0	0	0
Akers skeppslag	6.320	0	0	0
Värmdö skeppslag	9.798	0	0	0
Danderyd skeppslag	33.723	3	0,9	1
Sollentuna härad	13.251	5	3,8	1
Färentuna härad	6.841	1	1,4	0
Svarthöls härad	18.818	6	3,2	3
Öknebo härad	9.359	0	0	0
Sotholms härad	17.631	2	1,1	1
Södertälje	14.371	4	2,8	1
Sundbyberg	8.471	1	1,2	1
Djursholm	6.221	0	0	0
Lidingö	11.280	1	0,9	1
Vaxholm	2.975	0	0	0
Norrtilje	4.875	0	0	0
Östhammar	1.078	0	0	0
Öregrund	1.201	1	8,4	1
Sigtuna	1.931	0	0	0
Stockholms län:	264.909	45	1,7	28
<i>Upsala län:</i>				
Bro härad	2.977	1	3,5	1

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Häbo härad	4.392	4	9,0	4
Trögds härad	7.450	3	4,1	2
Åsmunda härad	5.178	0	0	0
Lagunda härad	4.027	4	10,0	2
Hagunda härad	4.900	5	10,2	4
Ulleråkers härad	7.489	3	4,1	3
Bälinge härad	3.743	0	0	0
Vaksala härad	5.226	2	3,8	1
Rasbo härad	3.732	2	5,4	2
Norunda härad	6.330	5	7,9	4
Olands härad	20.261	8	3,9	5
Örbyhus härad	26.260	12	4,6	8
Upsala	30.190	17	5,6	8
Enköping	5.896	2	3,4	1
Upsala län	138.060	68	4,9	45
<i>Södermanlands län:</i>				
Jönåkers härad	19.633	2	1,0	2
Rönö härad	11.004	2	1,9	2
Hölebo härad	6.002	1	1,6	1
Daga härad	8.626	1	1,1	1
Selebo härad	7.013	2	3,0	2
Akers härad	8.227	1	1,2	0
Österrekarne härad	12.291	7	5,7	6
Västerrekarne härad	8.921	2	2,1	2
Villåtinge härad	14.761	3	2,1	3
Oppunda härad	31.538	4	1,3	3
Nyköping	11.953	2	1,7	0
Katrineholm	7.805	1	1,3	0
Eskilstuna	32.674	6	1,9	5
Torshälla	1.826	0	0	0
Strängnäs	4.716	1	2,1	0
Mariefred	1.362	0	0	0
Trösa	800	0	0	0
Södermanlands län	189.182	35	1,9	27

Regierungsbezirk	Einwoh- nerzahl	Fälle von multipler Sklerose	Frequenz- zahl	Immer an demselben Ort an- sässig.
<i>Östergötlands län:</i>				
Finspånga länshärads tingslag	26.504	7	2,6	6
Bråbo härad	5.731	1	1,7	1
Memmings härad	9.024	4	4,4	4
Lösings härad	4.960	1	2,0	1
Östkind's härad	6.007	0	0	0
Björkekind's härad	4.159	2	4,8	1
Hammarkind's härad	17.301	3	1,7	2
Skärkind's härad	5.099	2	3,9	1
Åkerbo härad	3.063	0	0	0
Bankekind's härad	11.716	3	2,6	3
Hanekind's härad	7.437	3	4,1	0
Gullbergs härad	6.538	4	6,2	3
Valkebo härad	7.264	0	0	0
Bobergs härad	8.947	3	3,4	3
Aska härad	14.280	3	2,1	3
Dals härad	4.407	1	2,2	0
Lysings härad	9.465	2	2,2	2
Göstringe härad	14.630	3	2,1	1
Vifolka härad	7.066	4	5,6	2
Kinda härad	17.982	0	0	0
Ydre härad	7.559	4	5,2	4
Linköping	29.845	3	1,0	1
Norrköping	61.494	9	1,4	6
Söderköping	2.868	0	0	0
Motala	5.985	3	5,1	3
Vadstena	2.922	1	3,4	1
Skänninge	1.751	1	5,7	1
Mjölby	5.911	2	3,4	1
Östergötlands län	309.995	69	2,3	50
<i>Jönköpings län:</i>				
Södra Vedbo härad	14.576	5	3,5	4
Norra Vedbo härad	14.446	3	2,1	3
Vista härad	7.048	2	2,8	2
Tveta härad	19.792	6	3,0	6



Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässlg.
Mo härad	6.494	0	0	0
Västbo härad	31.621	11	3,4	9
Östbo härad	20.754	5	2,4	5
Västra härad	26.669	6	2,2	4
Östra härad	20.125	5	2,4	4
Jönköping	30.918	10	3,3	9
Huskvarna	8.156	1	1,3	1
Nässjö	9.113	0	0	0
Värnamo	4.054	2	5,0	1
Vetlanda	3.501	0	0	0
Eksjö	6.616	3	4,6	2
Tranås	6.436	3	4,7	3
Gränna	1.238	1	8,1	1
Jönköpings län	231.557	63	2,7	54
<i>Kronobergs län:</i>				
Uppvidinge härad	25.311	7	2,8	4
Konga härad	31.033	7	2,3	6
Kinnevalds härad	15.227	5	3,3	4
Norrvidinge härad	7.918	0	0	0
Allbo härad	28.630	7	2,5	5
Sumnerbo härad	37.717	14	3,8	12
Växjö	9.699	1	1,1	1
Kronobergs län	155.535	41	2,7	32
<i>Kalmar län:</i>				
Norra Tjusts härad	17.987	2	1,1	2
Södra Tjusts härad	19.397	3	1,5	0
Sevede härad	15.080	1	0,7	1
Tunäläns härad	10.519	0	0	0
Aspelands härad	14.811	1	0,7	1
Handbörds härad	15.981	1	0,6	1
Stranda härad	14.731	2	1,4	2
Norra Möre härad	11.285	3	2,6	2

Regierungsbezirk	Einwoh- nerzahl	Fälle von multipler Sklerose	Frequenz- zahl	Immer an demselben Ort an- sässig.
Södra Möre härad	35.923	7	2,0	7
Åkerbo härad	5.811	0	0	0
Slättbo härad	2.906	1	3,5	0
Runstens härad	3.590	0	0	0
Algutsrums härad	5.667	1	1,7	1
Möckleby härad	2.659	0	0	0
Gräsgårds härad	4.654	0	0	0
Kalmar	19.801	3	1,5	3
Oskarshamn	8.674	0	0	0
Västervik	12.611	0	0	0
Vimmerby	3.472	0	0	0
Borgholm	1.928	0	0	0
Nybro	4.011	1	2,5	0
Kalmar län	231.551	28	1,2	22
<i>Gotlands län:</i>				
Gotlands norra domsaga	24.553	2	0,8	2
Gotlands södra domsaga	22.428	0	0	0
Visby	10.467	0	0	0
Gotlands län	57.448	2	0,4	2
<i>Blekinge län:</i>				
Östra härad	25.806	3	1,2	3
Medelstad härad	30.008	4	1,3	3
Bräkne härad	22.004	7	3,2	7
Lister härad	24.327	3	1,2	0
Karlskrona	25.492	0	0	0
Ronneby	5.774	1	1,8	1
Karlshamn	7.487	2	2,7	0
Sölvesborg	3.943	2	5,1	2
Blekinge	144.841	22	1,5	16
<i>Kristianstads län:</i>				
Järrestad härad	9.568	1	1,1	1

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Ingelstad härad	26.692	8	3,0	7
Albo härad	10.076	0	0	0
Gärds härad	23.956	2	0,8	2
Villands härad	25.603	4	1,6	2
Östra Göinge härad	28.811	11	3,9	9
Norra Åsbo härad	29.736	6	2,0	5
Södra Åsbo härad	15.446	2	1,3	2
Bjäre härad	15.447	6	3,9	4
Västra Göinge härad	36.050	4	1,1	4
Kristianstad	13.515	1	0,7	1
Simrishamn	2.505	0	0	0
Ängelholm	5.269	1	1,9	0
Hässleholm	3.238	0	0	0
Kristianstads län	245.912	45	1,8	37
<i>Malmöhus län:</i>				
Luggude härad	48.216	13	2,7	8
Rönneberga härad	11.790	3	2,6	1
Onsjö härad	15.794	4	2,5	4
Harjagers härad	13.052	4	3,1	2
Torna härad	21.157	3	1,4	2
Bara härad	21.641	6	2,8	6
Oxie härad	21.997	10	4,6	9
Skytts härad	14.144	4	2,8	3
Vemmenhögs härad	21.691	8	3,7	5
Ljunits härad	5.877	2	3,5	2
Herrestads härad	7.081	2	2,8	2
Färs härad	23.544	11	4,7	11
Frosta härad	26.286	7	2,7	5
Malmö	127.870	21	1,7	15
Lund	24.512	6	2,5	5
Landskrona	18.534	4	2,2	2
Hälsingborg	55.889	8	1,5	5
Eslöv	6.035	2	3,4	1
Ystad	11.444	2	1,8	2
Trälleborg	13.014	2	1,6	0
Skanör-Falsterbo	1.097	0	0	0
Malmöhus län	510.664	122	2,4	90

Regierungsbezirk	Einwoh- nerzahl	Fälle von multipler Sklerose	Frequenz- zahl	Immer an demselben Ort an- sässig.
<i>Hallands län:</i>				
Höks härad	19.070	5	2,6	4
Tömmersjö härad	10.354	4	3,9	4
Halmstads härad	16.382	3	1,8	2
Ärstads härad	9.766	0	0	0
Faurås härad	16.227	1	0,6	1
Himle härad	12.379	0	0	0
Viske härad	5.961	2	3,0	1
Fjäre härad	17.332	2	1,2	1
Halmstad	23.866	3	1,2	2
Laholm	2.686	3	11,0	0
Falkenberg	5.527	1	1,9	1
Varberg	8.561	5	5,9	2
Kungsbacka	2.617	0	0	0
Hallands län	150.128	29	2,0	18
<i>Göteborgs-Bohus län:</i>				
Askims härad	20.996	1	0,5	1
Hisinghs härad	12.672	0	0	0
Inlands Södra härad	6.781	0	0	0
Inlands Torpe härad	4.800	2	4,1	2
Inlands Nordre härad	8.980	3	3,4	3
Inlands Fräkne härad	4.509	0	0	0
Orust östra härad	5.339	2	3,6	2
Orusts västra härad	11.245	1	0,8	1
Tjörns härad	9.125	2	2,2	2
Lane härad	7.882	2	2,6	2
Stångenäs härad	9.688	0	0	0
Sotenäs härad	14.094	1	0,7	1
Tunge härad	7.594	0	0	0
Sörbygdens härad	3.432	2	5,9	2
Bullarens härad	3.182	1	3,8	1
Kville härad	6.943	1	2,7	1
Tanums härad	8.063	2	2,5	2
Vette härad	11.468	2	1,8	2
Sävedals härad	10.115	1	1,0	1

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Göteborg	243.690	55	2,3	32
Mölnadal	17.555	2	0,6	1
Kungälv	2.381	0	0	0
Marstrand	1.646	0	0	0
Lysekil	5.866	1	1,6	1
Uddevalla	15.104	2	1,3	1
Strömstad	3.073	2	6,6	2
Göteborgs-Bohns län:	457.067	85	1,9	60
<i>Älvsborgs län:</i>				
Tössbo härad	6.796	3	4,3	3
Vedbo härad	21.762	7	3,2	6
Valbo härad	10.226	2	2,0	2
Nordals härad	10.396	1	0,9	0
Snudals härad	11.915	4	3,4	4
Väne härad	13.362	6	4,3	5
Bjärke härad	4.704	3	6,4	1
Flundre härad	6.748	2	3,0	2
Ale härad	13.511	2	1,3	2
Vättle härad	10.769	4	3,6	4
Kollings härad	15.587	5	3,2	5
Gälsene härad	8.529	0	0	0
As härad	10.328	5	4,9	5
Vedens härad	6.656	0	0	0
Bollebygdens härad	7.500	1	1,3	0
Marks härad	34.378	7	2,0	7
Kinds härad	28.665	10	3,3	9
Redvägs härad	9.399	2	2,2	2
Vänersborg	8.942	5	5,6	4
Trollhättan	15.018	3	1,8	3
Alingsås	8.870	1	1,2	1
Borås	38.236	7	1,6	5
Ulricehamn	4.138	0	0	0
Ämål	6.764	1	1,3	1
Älvsborgs län	313.199	80	2,6	71

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
<i>Skaraborgs län:</i>				
Ase härad	5.766	2	3,4	2
Viste härad	9.559	8	8,4	7
Barne härad	11.938	5	4,2	4
Laske härad	5.750	3	5,2	3
Källands härad	12.070	4	3,8	4
Kinnefjärdings härad	7.156	1	1,4	1
Kinne härad	11.922	5	4,2	4
Valle härad	5.681	0	0	0
Skänings härad	12.917	6	4,7	6
Vilske härad	5.663	4	7,1	4
Frökinds härad	2.184	2	9,2	1
Vartofta härad	26.667	5	1,9	4
Gudhems härad	10.678	2	1,9	2
Kåkind's härad	15.494	3	1,9	3
Vadsbo södra tingslag	52.117	8	1,3	6
Vadsbo norra tingslag				
Mariestad	6.143	2	3,3	2
Lidköping	9.296	4	4,4	4
Skara	6.770	2	3,0	2
Skövde	10.838	1	0,9	0
Hjo	2.758	3	11,0	2
Tidaholm	4.816	1	2,1	1
Falköping	6.736	5	7,3	3
Skaraborgs län	242.329	76	3,1	66
<i>Värmlands län:</i>				
Färnebo härad	16.845	3	1,8	3
Visums härad	6.517	2	3,1	2
Ölme härad	4.175	2	4,8	2
Väse härad	7.175	2	2,8	2
Karlstads härad	15.899	6	3,8	0
Kils härad	18.938	7	3,7	6
Grums härad	10.507	4	3,8	4
Näs härad	13.709	4	2,9	2
Gillberga härad	13.352	8	6,0	8
Nordmarks härad	18.778	3	1,6	3

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Jösse härad	27.273	3	1,1	3
Frykdals härads övre	13.040	6	4,6	6
Frykdals härads nedre	20.630	8	3,9	7
Älvdals härad	31.407	7	2,2	7
Nyeds härad	5.743	1	1,8	0
Karlstad	20.911	6	2,8	5
Krstinhamm	12.434	0	0	0
Fllpstad	4.632	0	0	0
Arvika	7.979	3	3,8	3
Värmlands län	369.945	75	2,8	63
<i>Örebro län:</i>				
Örebro härad	22.262	3	1,4	3
Glanhammar härad	6.590	3	4,6	3
Askers härad	9.344	4	4,4	4
Sköllersta härad	9.320	3	3,3	2
Knnla härad	19.780	6	3,0	6
Hardemo härad	2.311	0	0	0
Grhstens härad	7.003	0	0	0
Sundbo härad	9.439	3	3,2	3
Edsbergs härad	13.305	5	3,8	4
Karlskoga härad	21.923	10	4,5	8
Grythytte-Hällefors härad	8.992	2	2,3	2
Nora-Hjulsjö härad	9.816	1	1,1	1
Fellugsbro härad	10.864	4	3,7	4
Lindes-Ramsbergs härad	12.256	6	4,9	5
Nya Kopparbergs härad	10.534	0	0	0
Örebro	37.523	11	3,0	7
Askersund	2.102	0	0	0
Nora	2.631	2	7,7	2
Lindesberg	3.242	1	3,1	1
Örebro län	219.236	64	2,9	55
<i>Västmanlands län:</i>				
Akerbo härad	16.901	3	1,2	3
Skinnskattebergs härad	6.755	3	4,3	2

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Snevringe härad	19.298	4	2,1	4
Gamla Norbergs bergslag	15.600	3	1,9	1
Vangsbros härad	3.926	1	2,6	1
Norrbros härad	6.138	0	0	0
Tuhundra härad	2.850	1	3,6	1
Siende härad	5.384	0	0	0
Yttertjurbo härad	21.176	2	1,0	0
Övertjurbo härad	7.210	2	2,9	1
Simtuna härad	10.892	5	4,6	4
Torstuna härad	4.678	2	4,4	1
Våla härad	9.631	4	4,2	4
Västerås	30.378	3	1,0	0
Sala	8.022	0	0	0
Köping	6.395	0	0	0
Arboga	4.772	0	0	0
Västmanlands län	161.708	33	2,1	22
<i>Kopparbergs län:</i>				
Folkare härad	15.404	1	0,7	1
Hedemora härad	19.914	1	0,5	1
Falu domsaga Norra tgl	21.141	7	3,3	6
Falu domsaga Södra tgl	31.359	10	3,2	10
Västerbergslags domsaga	29.872	4	1,4	3
Nås tingslag	15.275	1	0,7	1
Malungs tingslag	13.747	1	0,7	1
Leksands-Gagnefs tgl	24.368	7	2,9	7
Rättviks tingslag	14.294	3	2,1	3
Orsa tingslag	8.423	0	0	0
Mora tingslag	16.998	2	1,2	1
Älvdals tingslag	5.831	1	1,7	1
Särna-Idre tingslag	3.460	0	0	0
Falun	13.370	7	5,3	6
Säter	2.176	1	4,6	0
Hedemora	3.800	2	5,3	1
Avesta	5.165	0	0	0
Ludvika	5.050	2	4,0	2
Kopparbergs län	249.647	50	2,0	44



Regierungsbezirk	Einwoh- nerzahl	Fälle von multipler Sklerose	Frequenz- zahl	Immer an demselben Ort an- sässig.
<i>Gävleborgs län:</i>				
Gästriklands västra domsaga	30.793	9	2,9	6
Gästriklands östra domsaga	44.397	10	2,3	8
Ala tingslag	26.952	3	1,1	3
Enångers härad	7.513	0	0	0
Bollnäs domsaga	36.886	2	0,5	2
Västra Hälsinglands doms.	37.941	4	1,1	3
Delsbo tingslag	10.837	3	2,8	2
Bergsjö-Forså tingslag	26.433	3	1,2	3
Gävle	38.868	9	2,3	6
Söderhamn	11.643	1	0,8	1
Hudiksvall	7.321	1	1,4	1
Gävleborgs län	279.588	45	1,6	35
<i>Västernorrlands län:</i>				
Medelpads västra domsaga	39.044	2	0,5	2
Njurunda-Sköu-Ljustorps tgl.	49.641	4	0,8	4
Indals tingslag	6.853	0	0	0
Ångermanlands södra doms.	46.041	5	1,1	5
Boteå tingslag	14.375	0	0	0
Sollefteå tingslag	13.551	1	0,7	1
Ramsele-Resele tingslag	14.494	2	1,4	2
Fjällsjö tingslag	12.757	2	1,6	2
Ångermanlands norra doms.	46.872	11	2,4	11
Härnösand	11.787	0	0	0
Sundsvall	18.006	2	1,1	2
Sollefteå	2.735	0	0	0
Örnsköldsvik	5.032	0	0	0
Västernorrlands län	278.503	29	1,1	20
<i>Jämtlands län:</i>				
Ragunda tingslag	15.092	4	2,7	4
Revsund-Brunflo-Näs tgl	17.050	2	1,2	2
Lit-Rödöns tingslag	18.902	3	1,6	3

Regierungsbezirk	Einwohnerzahl	Fälle von multipler Sklerose	Frequenzzahl	Immer an demselben Ort ansässig.
Hammerdals tingslag	17.901	3	1,7	3
Undersåker-Offerdals tgl	17.135	4	2,3	3
Sunne-Oviken-Hallens tgl	11.230	1	0,9	1
Bergs tingslag	7.080	1	1,4	1
Hede tingslag	5.632	3	5,4	3
Svegs tingslag	10.340	3	2,9	3
Östersund	14.138	1	0,7	1
Jämtlands län	134.500	25	1,9	24
<i>Västerbottens län:</i>				
Nordmalings-Bjurholms tgl	18.400	5	2,7	4
Degerfors tingslag	9.277	3	3,3	3
Umeå tingslag	29.613	14	4,7	12
Nysätra tingslag	16.274	12	7,4	11
Burträsk tingslag	9.923	1	1,1	1
Skellefteå tingslag	45.217	17	3,8	15
Norsjö-Malå tingslag	10.628	0	0	0
Lycksele tingslag	25.376	3	1,2	3
Åsele-Vilhelmina tingslag	22.986	2	0,9	2
Umeå	11.138	3	2,7	2
Skellefteå	5.203	3	5,9	3
Västerbottens län	204.035	63	3,1	56
<i>Norrbottens län:</i>				
Piteå-Älvsby tingslag	30.725	3	1,0	2
Arvidsjaurs tingslag	8.948	1	1,2	1
Arjeplog lappmarks tingslag	3.795	1	3,8	1
Nederluleå tingslag	12.980	0	0	0
Överluleå tingslag	12.961	1	0,7	1
Jokkmokks tingslag	7.530	0	0	0
Råneå tingslag	8.750	1	1,2	0
Överkalix tingslag	7.396	1	1,4	1
Nederkalix tingslag	18.004	4	2,2	4
Torneå tingslag	14.467	1	3,7	0
Pajala-Korpilombolo tingslag	10.928	0	0	0

Regierungsbezirk	Einwoh- nerzahl	Fälle von multipler Sklerose	Frequenz- zahl	Immer an demselben Ort an- sässig.
Gällivare lappmarks tingslag	20.228	4	2,0	3
Jukkasjärvi lappmarks tgl	18.576	1	0,5	1
Karesuando lappmarks tgl	1.086	0	0	0
Luleå	11.334	0	0	0
Piteå	3.102	1	3,3	1
Boden	6.517	1	1,6	0
Haparanda	2.519	2	8,0	2
Norrbottens län	199.825	22	1,1	17

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CXXXVIII

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THE Cl-ION CONTENT OF  
THE CEREBROSPINAL FLUID AND ITS  
RELATION TO THE Cl-ION CONTENT  
OF THE BLOOD

BY

*FRITZ KARLSTRÖM*

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HELSINGFORS 1942. MERCATORS TRYCKERI

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HUMAN GENETICS AND RACE BIOLOGY, UPPSALA  
(HEAD: PROFESSOR G. DAHLBERG).

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## FOREWORD

The purpose of the present work is to try to determine the diagnostic value, firstly, of the Cl-ion content of the cerebrospinal fluid, and secondly, of the relation between the Cl-ion content of the fluid and that of the blood, and also to decide whether these investigations afford more of diagnostic value than determinations of the sugar content of the fluid and the sugar index.

With some interruptions, the work has been in progress during the last three years. The material has been obtained from the following hospitals in Stockholm: Crown Princess Lovisa's Hospital for Children, The Norrtull Hospital, The Children's Hospital Samariten, The Sachs Children's Hospital, The Stockholm Epidemic Hospital, The S:t Eriks Hospital the neurological and neurosurgical clinics of the Seraphim Hospital and the Stora Sköndal Home for Epileptics.

The investigations have been carried on chiefly at the Crown Princess Lovisa's Hospital for Children. I owe a great debt of gratitude to its superintendent, Professor A. LICHTENSTEIN, for his help in planning the work and for his kindly advice and criticism while it was in progress. The statistical part of the work has been carried out at the State Institute of human Genetics and race Biology at Uppsala. I have to thank Professor G. DAHLBERG, its head, not only for the statistical working-up, but also for much valuable advice. I proffer my thanks to Dr G. NORBERG of the Chemical Intitution of the Caroline Institute for his help in planning the chemical analyses.

I owe a great debt of gratitude to the heads of the above hospitals, i. e. Professor A. LICHTENSTEIN, Docent C. W. HERLITZ, Docent N. MALMBERG, Docent C. GYLLENSWÄRD, Docent R. BERG-



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# A SURVEY OF THE LITERATURE.

## Introduction.

Already in ancient times it was known that the ventricles of the brain were filled with a fluid, but the study of this fluid is of relatively recent date. In the literature from the 18th century there are certainly isolated statements that the central nervous system is laved by a clear fluid (CORUGNO, 1769), but the first real study of the localisation of that fluid, its circulation and function are ascribed to MAGENDIE (1825). During the 19th century, research workers later than Magendie investigated the fluid, principally from animals and dead persons. The majority of cerebrospinal fluids from living persons were obtained from children with hydrocephalus, whose cerebral ventricles were punctured with trocars. (CONQUEST 1840, SCHMIDT 1850, TOISIN and LENOBLE 1891, DIRCKSEN 1901). Another method of obtaining the cerebrospinal fluid was to puncture the spina bifida (STSCHERBAKOFF 1870, GRIMBERT 1891). In 1902 ZDAREK described how he obtained cerebrospinal fluid from a woman who was operated on for a pelvic tumour, which was found, however, to be a meningocele spinalis anterior and contained an abundance of fluid.

An important date in the history of c. s. fluid research is the year 1891, when QUINCKE introduced the lumbar puncture. A decade passed, however, before this method of investigation became generally known and employed. At first it was mainly the internists, and later also the neurologists, that were interested in it, but gradually it came into use within almost all the special fields of medicine.

As early as in 1906 WESTENHÖFER conceived the possibility of a cistern puncture, but his suggestion was not taken up until 1919, when AYER, ESSICH and WEGEFORT performed the puncture for the

first time. Since then this method of investigation has superseded lumbar puncture in many quarters. During recent years puncture of the ventricles has also become a clinical routine method, though mainly within diagnostics for cerebral tumours.

The chemical composition of the c. s. fluid has been the subject of extensive research work during the last century. As new substances could be proved in the fluid, and the amounts of them, in health and in different morbid conditions, could be determined quantitatively, the literature on the subject has grown and will now have attained vast proportions. One of the first substances that could be proved in the c. s. fluid was NaCl, thanks to the fact that the method for proving it, and its quantitative determination, at least roughly, is simple.

## Methods.

The statements found in earlier, but also in more recent, literature as to the content of Na Cl in the c. s. fluid and the blood are based on methods which really do not afford information as to the amount of NaCl but only as to the content of Cl-ions. This is probably of no great practical importance, but it must be remembered that, although the Na-ion is predominant, there are also other chlorides than NaCl in both the fluid and the blood.<sup>1</sup>

In earlier times a certain quantity of fluid was dried for chloride determinations, and the water-soluble salts were extracted with water, the chlorides being determined by means of titration with Ag NO<sub>3</sub>, with potassium chromate as the indicator. Subsequently VOLLHARD'S (1878) method was introduced, all the chlorides being

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<sup>1</sup> The best work on the subject is that by ABRAMSON (1930). He found the following mean values for normal cases: Na 332.8 mg per 100 cm<sup>3</sup>. K. 13.74 mg per 100 cm<sup>3</sup>, Ca 5.24 mg per 100 cm<sup>3</sup> and Mg 2.4—3.0 mg per 100 cm<sup>3</sup>.

Thus, according to RICHTNER and QUITTNER (1922), the fluid contains 30—95 mg per 100 cm<sup>3</sup> of potassium and 256—517 mg per 100 cm<sup>3</sup> of sodium. LICKINT (1926) found the Ca in the fluid to vary between 5.2 and 8.6 mg per 100 cm<sup>3</sup>, and NEAL and ESSLEMONT (1928) between 4.8 and 10.0 mg per 100 cm<sup>3</sup>. EISLER (1928) found the following values: K. 12.97—13.47 mg per 100 cm<sup>3</sup>, Ca 4.92—5.64 mg per 100 cm<sup>3</sup> and Mg 1.02—1.3 mg per 100 cm<sup>3</sup>.

For blood the *Handbuch der Biochemie der Menschen und der Tiere* (1936) gives (according to a table by HEUBNER) Na 280—320 mg per 100 cm<sup>3</sup>, K 16—24 mg per 100 cm<sup>3</sup>, Ca 8—16 mg per 100 cm<sup>3</sup>, Mg 1—4 mg per 100 cm<sup>3</sup>.

precipitated as  $\text{AgCl}$  by the addition of an excess of  $\text{Ag NO}_3$ , and this was titrated back with rodanid. BANG's (1920) micro-method was widely used during the first decades of the 20th century, and many authors during the 1920's and 1930's used RUSZNYAK's micro-method, published in 1920. These last two methods have been compared with one another by, *inter alia*, JACOBOWSKY (1929), who found greater errors of measurement in the latter than in the former. Another method very largely used is VAN SLYKE's, published in 1923, which was modified by REHBERG (1926) and improved by WILSON and BALL (1928).

A method in which the final stage of the titration is obtained on an entirely different principle from that of the methods mentioned above, is the electrometric method according to E. MÜLLER (1926). For determinations of the  $\text{Cl-ion}$  content this has been used by, *inter alia*, STRÖM (1935, blood, urine and gastric juice), KARLSSON and NORBERG (1936, blood), SUNDBERG (1938, milk), and IHRE (1938, gastric juice). In my investigations I have used the same method, which, as far as I can find, has not been used earlier for determinations of the  $\text{Cl-ion}$  content in the c. s. fluid. In the majority of works on the  $\text{Cl-ion}$  content of the fluid, with extremely few exceptions, *e. g.*, JACOBOWSKY (1929), the standard error of the method used have not been stated.

## Some circumstances who may influence the content of chlorides in the c. s. fluid.

*To what extent does the supply and loss of chlorides influence their content in the c. s. fluid?*

The extremely interesting and much discussed question of the physiology of c. s. fluid formation will not be taken up for closer examination in these pages. I would only mention that three main theories on the formation of the fluid have been discussed. According to the first, the fluid is formed by means of the secretion of the cells in the plexus choreoideus, according to the second by a transudation of the constituent parts of the blood through the vessel walls, and according to the third by a dialysis, the wall between the blood and the fluid being said to be a semipermeable membrane, and

the transmission of dissolved substances being regulated according to physico-chemical laws. Which of these theories is correct has not been elucidated. There is a general tendency to accept the last-mentioned theory (cf. for example, WALTER 1929). Even though an activity more or less resembling a secretion plays a part in the formation of the fluid, the diffusion processes will inevitably assert themselves, at any rate so far as secretion processes are played off against diffusion processes. For such an easily diffusible substance as NaCl the Donnan effect must assert itself, at least to a certain degree, and there must be a diffusion balance, although naturally it need not be perfect, between the blood and the fluid. This is the reason why many authors have determined the relation between the chlorides in the fluid and the blood, and considered that quota to have a greater value than the content of chlorides in the fluid alone. One therefore asks oneself in what degree factors which influence the quantity of Cl-ions in the blood (e. g. the supply of NaCl, the loss of chlorine owing to vomiting, diarrhoea, sweating, the tapping of ascites and pleura exudates) also influence the chlorides in the fluid. The statements on the subject which I have been able to find in the literature are meagre.

TSCILOW and SAPRANOFF (1932) examined the chloride content of the blood and the c. s. fluid in 18 cases of various nervous diseases. The patients were then given 10 g of NaCl per os, and, after periods varying between 1 hour 25 minutes and 8 hours 25 minutes, the chloride examinations were repeated. It was found that in 10 cases the chlorides in the blood had increased and in 11 cases in the fluid, and that no agreement between the increase in the blood and that in the fluid could be established. The authors draw the conclusion that there is a certain amount of independence between the chloride content of the blood and that of the fluid. The objections may be raised against this conclusion firstly, that the material on which the authors base their conclusions is somewhat scanty and secondly, that the conclusion is somewhat diffusely formulated. A statement that there is a certain amount of independence does not contribute very much to elucidating the situation, unless a definite expression for the extent to which the fluid is dependent on the blood can be obtained. In other words more definite numerical information is called for.

KUBIE and SCHULTS' (1925) experiments on dogs are interesting. During cistern drainage 6.5 g of NaCl were administered intravenously in hypotonic solution, and specimens of blood and c. s. fluid were taken every 10 minutes. It proved that the Cl-ion content of the blood hardly changed during the hour following the injections. On the other hand the Cl-ion content of the fluid decreased, in one case from 698 to 607 mg per 100 cm<sup>3</sup> and in another case from 725 to 687 mg per 100 cm<sup>3</sup>. The authors state that this great decrease is due to the following circumstances: By the administration of the hypotonic solution the blood proteins are diluted. In conformity with DONNAN's law the Cl-ions are carried from the tissues of the body and from the c. s. fluid to the blood, so that the Cl-ion content of the latter remains fairly constant, while the Cl-ion content of the fluid decreases. If a hypotonic glucose solution is given intravenously the Cl-ion content of both the blood and the fluid decreases and subsequently increases slowly. This restoration of the Cl-ion content takes place more slowly in the fluid than in the blood, which, according to the authors, is due to the specimens of the fluid not having been taken from the place where the fluid is formed, but from the cisterna magna, which the fluid requires a certain time to reach. The author's conclusion is: On the whole the concentration of chloride and glucose in the fluid follows the concentrations of the substances in the blood. This conclusion is also formulated vaguely. That the concentrations follow each other on the whole implies that they are dependent on each other, which of course does not exclude their being, in fact, to some extent independent of each other. In other words, the conclusion is all too indefinite, and just because definitive conclusions have not been reached, it may be claimed that KUBIE and SCHULTS' experiments do not conflict with TSCHILOW and SAPRJANOFF's results.

DOBREFF and SAPRJANOFF (1932) established permanent drainage in five cases of nervous diseases. The patients had not partaken of food for 12 hours, and during the experiment, which lasted for 24 hours, did not even drink any water. During the 24 hours of the experiment the chloride, sugar, and leukocyte contents of the c. s. fluid were examined 8 times. It was found that, during the night and the morning hours, the chloride content was lower than during the later part of the 24 hours. The greatest day variation in the

chloride content amounted to about 10 %. The curve for the sugar content during the 24 hours for the fasting patients was on the whole a reflection of the curve for the Cl-ion content, i. e. with high night and morning values. To what extent the permanent drainage affected the Cl-ion and sugar contents cannot be judged. The chloride values obtained are extremely high (c. 800—900 mg NaCl per 100 cm<sup>3</sup>), and do not agree with what other investigators have found for these diseases.

*Is there any difference in the chloride content of the lumbar, cistern and ventricle fluids?*

Although it is not yet fully elucidated where the c. s. fluid is formed, all appear to be agreed that the Plexus Choriodeus is its main source. The fluid flows from the lateral ventricles of the brain through the Foramen Monroi to the 3rd ventricle, through the Aqueductus Sylvii to the 4th ventricle, and through Luschke's foramen and Magendie's foramen to the Cisterna Magna, and then up into the subarachnoidal spaces on the convexity of the brain and also down into the spinal canal. It is considered that the fluid is absorbed chiefly through the Villi Arachnoideus and the lymphatic spaces, both in the brain and in the spinal canal. Owing to these circumstances it is *a priori* hardly probable that the composition of the fluid is identically the same in all parts of the fluid-conveying spaces. Thus, according to several authors (CESTAN, RISER and LABORDE, 1923, MALYKIN, 1930) the cell and albumin contents clearly increase in the order, ventricle, cistern and lumbar fluids, while the sugar content shows a contrary state of things. The following investigations throw light upon the question as to whether there is any difference between the ventricle, cistern and lumbar fluids concerning the NaCl content.

CESTAN, RISER and LABORDE (1923) state that in a healthy person both the ventricle and lumbar fluids contain 730 mg per 100 cm<sup>3</sup> of NaCl. FREMONT-SMITH and DAILEY (1925) found the same chloride concentration in the ventricle, cistern and lumbar fluids in one person. STEWART (1928) examined the lumbar and cistern fluids in 35 healthy children and found that the mean content of Na Cl in the former was 706 mg per 100 cm<sup>3</sup> and in the latter 707 mg per 100 cm<sup>3</sup>. In 9 cases he examined the lumbar, cistern and ventricle fluids and found the content of NaCl to average 681, 682

and 681 mg per 100 cm<sup>3</sup> respectively. MALYKIN (1930) examined, *inter alia*, 14 cases of meningitis and found that the Cl-ion concentration was lower in the lumbar than in the cistern fluid. With fractional lumbar puncture in 7 pathological cases HAUG and GÖTTKE (1933) found, in 5 cases, the first, and, in two cases, the last fluid evacuated poorer in chlorides. In 11 cases with normal fluids and 1 case with slight pathological changes in the fluid, LEIPOLD (1935) found the lumbar fluid richer in chlorides than the cistern fluid in all the cases but one. The difference amounted to between 4 and 35 mg per 100 cm<sup>3</sup> of NaCl. CHRISTIANSEN (1936) examined 33 cases of suspected or definite cerebral tumours. 25 of these had been punctured in the ventricle and 8 in the cistern. The NaCl content averaged 734.5 mg per 100 cm<sup>3</sup> in the former and 724.7 mg per 100 cm<sup>3</sup> in the latter. The dispersion in his figures is great. The investigation affords no support for the claim that the Cl-ion content is different in the ventricle and cistern fluids.

From the above it appears that statements about the content of Cl-ions in the ventricle, cistern and lumbar fluids differ and to some extent contradict each other. STEWART'S (1928) investigations appear to me to be most reliable. He found no difference in the Cl-ion content of the fluids mentioned. His material is considerable and comprises healthy children (each was examined carefully). The method employed is not stated, however, and consequently the margins of error are not known. Above all, this investigation indicates that there is no great difference between the Cl-ion content of the cistern fluid and that of the lumbar fluid; but the investigations made hitherto do not exclude the possibility of small differences, so that the problem may deserve further investigation.

#### *Age and the Cl-ion content of the c. s. fluid.*

From investigations, in the first place those by WAITZ (1928) and SAMSON (1930), it is known that in the new-born and also during the child's first months of life, the c. s. fluid is more abundant in cells and albumin, has a higher albumin coefficient, and in general a more varying and lower sugar content, than in older children and adults. Not until the latter part of the first six months of life has the fluid the same composition as that of adults in the respects mentioned. With regard to the content of NaCl in the fluid during the first year of life in children, SAMSON (1930)



states that, during the new-born period, it is low, and that values down to 640 mg per 100 cm<sup>3</sup> are not rare. During the child's first three months the NaCl content varies between 640 and 720 mg per 100 cm<sup>3</sup> though the low values are rare. STEWART (1928) examined healthy children of different ages and found the following values for the lumbar fluid: The new-born period (1 case) 670 mg per 100 cm<sup>3</sup>, first three months (9 cases) average 688 mg per cm<sup>3</sup>, 4—6 months (4 cases) average 705 mg per 100 cm<sup>3</sup>, over 6 months (36 cases) average 715 mg NaCl per 100 cm<sup>3</sup>. The correlation between age and the chloride content of the fluid in these 36 cases is  $= 0.32 \pm 0.15$ , and thus, according to this investigation, there is no significant correlation. I have not been able to find any other investigations into the correlation between the Cl-ion content of the fluid and the patient's age (if the high ages when arteriosclerosis asserts itself are excluded. However, WALTER (1929) states that even during the later part of life the chemical composition of the fluid is not changed). As, after the age of 6 months, the fluid does not differ in all the respects investigated from that of older children and adults, there is no reason whatever to suppose that the Cl-ion content of the fluid forms an exception.

## The chloride content of the c. s. fluid according to old investigations.<sup>1</sup>

In the introduction it was mentioned that it has been known for a very long time that the c. s. fluid contains NaCl. As the methods for its quantitative determination have been improved, the results have naturally become more certain. Investigations from

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<sup>1</sup> The content of chlorides in the fluids of the body are sometimes given in the literature as mg NaCl per 100 cm<sup>3</sup>, which, as has been mentioned above, is not quite correct, sometimes as mg chloride per 100 cm<sup>3</sup>, and sometimes as mmol of Cl-ions. I recall the following fact: the molecular weight of Na is 23.0, of Cl 35.5 and thus of NaCl 58.5. To recalculate from mg NaCl per 100 cm<sup>3</sup> to mg chloride per 100 cm<sup>3</sup>, multiply by  $\frac{35.5}{58.5}$ , and from mg chloride per 100 cm<sup>3</sup> to mmol Cl-ions multiply by  $1/35.5$ .

It has been most usual to give the chloride content as mg NaCl per 100 cm<sup>3</sup>. For the sake of surveyability I have therefore, both above and in the continuation of the review of the literature, retained this method of indicating the chloride content and recalculated mg chloride per 100 cm<sup>3</sup> and mmol of Cl-ions to mg NaCl per 100 cm<sup>3</sup>. On the other hand, in the results of my

Table 1.

The NaCl content of the c.s. fluid according to old investigations.

Author	Year	Diagnosis	No. of cases	NaCl in mg per 100 cm <sup>3</sup>	Remarks
CONQUEST	1840	Hydrocephalus	19	845	
SCHMIDT	1850	Hydrocephalus	2	868—882	As «inorganic substance»
STSCHERBAKOFF	1870	Spina bifida	1	542—688	On 3 different occasions
TOISON and LENOBLE	1891	Hydrocephalus	1	830—850	On 2 occasions.
" "	"	Skull injury	1	875—880	As «inorganic substance».
GRIMBERT	"	Spina bifida	1	669	
DENIGÈS and SABRAZES	1896	Meningitis tbc.	3	590—600	
" "	"	Rabies	1	590	
DIRCKSEN	1901	Healthy individual	4	550—575	
"	"	Various diseases	23	525—675	
ARCHARD, LAEPER and LAUBRY	"	Various diseases, mainly «pain in the hip», shingles and meningitides	45	525—766	
MONOD	1902	?	?	700—800	
ZDAREK	1902	Meningocele spinal. ant.	1	700	
NOUBÉCOURT and VOISIN	1903	Various diseases	12	715—792	
" "	"	Congenital syphilis	25	673—840	New-born
" "	"	Otitis	14	777—790	
" "	"	Meningitis tbc.	7	594—694	
" "	"	Bronchopneumonia	25	670—820	
VOISIN, J. and R.	1910	Epilepsy	24	678—796	

investigations I have, like HAMILTON (1925), FREMONT-SMITH and co-workers (1931) etc., and in conformity with the present usage within chemistry given the Cl-ion content in mmol. In the conclusions, however, the mmol figures have been converted into figures representing mg NaCl per 100 cm<sup>3</sup>. This has been done so that the results of earlier investigators may be easily compared with mine.

For comparisons of the chloride content of the c. s. fluid and that of blood, a number of authors have determined the latter in serum, others in whole blood. The difference in the content of chlorides in serum and blood is substantial, since the red blood corpuscles contain considerably less chlorides than does serum. [According to VAN SLYKE, WU and McLEAN (1923)] the NaCl content of the red blood corpuscles is about 50 %, and according to SNAPPER (1913) about 40 % of the content in serum.

the 19th century and the first part of the 20th century really dealt only with pathological cases. These investigations are now principally of historical value, but their results are collocated below in tabular form.

It is seen from the table that the figures of different authors for the NaCl content of the c. s. fluid vary very considerably. The approximate NaCl content can be seen, however, and it may be observed that it is reduced in a number of pathological cases and possibly increased in others. For example, DIRCKSEN (1901) divides his material into normal cases (550—600 mg NaCl per 100 cm<sup>3</sup>), diseases accompanied by reduced NaCl contents e. g. meningitis, tbc., hydrocephalus, paralysie generale, variola (525—575 mg NaCl per 100 cm<sup>3</sup>), and diseases accompanied by an increased NaCl content, e. g. eclampsia, uraemia, pneumonia, typhus (605—675 mg NaCl per 100 cm<sup>3</sup>).

### The chloride content of the c.s. fluid and its relation to the chloride content of blood and serum in the normal condition.

The investigations which have been carried out on the chloride content of the c. s. fluid from healthy persons are somewhat few in number, for the simple reason that it has not been considered that lumbar and cistern punctures ought to be performed on perfectly healthy persons.

In his monograph of 1919 on the lumbar fluid, ESKUCHEN states that the NaCl content of the fluid is normally 725—750 mg per 100 cm<sup>3</sup> and may amount to 800 mg per 100 cm<sup>3</sup>. He does not say upon what investigations his statements are based. RICHTNER-QUITTNER (1922) examined 3 «normal cases» and found the NaCl content of the fluid to vary between 606 and 698 mg per 100 cm<sup>3</sup>. CSÁKI (1924) employed KORÁNYI-RUSZNYAK's micromethod in 20 normal cases (»hauptsächlich negativer Luesverdacht und funktionelle Nervenfälle»). His values lie between 684 and 731 mg per 100 cm<sup>3</sup>. NOWICKE's (1924) 25 adult women, who had been operated for gynecological tumours under lumbar anesthesia, and 2 healthy children, showed NaCl values in the fluid varying between 710 and

760 mg per 100 cm<sup>3</sup>. LICKINT (1928) bases himself on a material which, as far as I have been able to find, is the largest which has been published (450 lumbar fluids examined). 70 of the patients were »praktisch als normal zu bezeichnenden Fällen». They exhibited a NaCl content between 704 and 787 mg per 100 cm<sup>3</sup>, and the majority one between 720 and 775 mg per 100 cm<sup>3</sup>. The mean figure was 741 mg per 100 cm<sup>3</sup>. He employed a modification of VOLLHARD's method worked out by NEUBAUER. A work published by FREMONT-SMITH, DAILEY, MERRITT, CARROLL and THOMAS (1931) is based on a large material of cerebrospinal fluids (240). 22 of their patients who had normal fluids and had fasted for 9 hours, exhibited a NaCl content varying between 696 and 746 mg per 100 cm<sup>3</sup>. The mean figure was 726 mg per 100 cm<sup>3</sup>. None of the patients were considered healthy, and their diagnoses were extremely varied (pulm. tuberculosis, epilepsy, syphilis in the central nervous system, diabetes insipidus, etc.). CAFFEY, McLEAN and SULLIVAN (1927) found the NaCl content to vary between 675 and 750 mg per 100 cm<sup>3</sup> (the number of cases not indicated). HENDRY (1939) examined 40 children, who showed no signs of meningeal irritation but were suffering from, *inter alia*, vomiting, diarrhoea, convulsions. The NaCl in the fluid varied in these cases between 635 and 770 mg per 100 cm<sup>3</sup>.

Definitely the best investigation is STEWART's (1928), on 50 children who were examined carefully and found to be entirely healthy before the lumbar punctures. The mean figure for them all was 709 mg per 100 cm<sup>3</sup>. 36 of them were between 6 months and 12 years of age, and in them the NaCl content of the fluid varied between 679 and 763 mg per 100 cm<sup>3</sup> and averaged 715 mg per 100 cm<sup>3</sup>.

As appears from the above, statements as to the NaCl content of the fluid in normal cases varies roughly between 600 and 800 mg per 100 cm<sup>3</sup>. These wide limits will be largely due to the fact that ideas vary as to the conditions for what can be called normal cases. The material of FREMONT-SMITH and *his co-workers* (1931) does not of course satisfy the conditions, and their statements have only been included because they are often cited in the literature. None of the authors referred to have indicated what examinations were made before the patients were declared healthy, nor have they

described the details of the investigation arrangements (how the puncturing needles were boiled, how long and in what manner the fluids were stored before they were examined, etc.), and further, they have not mentioned whether double tests were taken, nor the standard error of the methods employed. In my opinion LICKINT's (1928) and STEWART's (1928) investigations appear to be most reliable. As has been mentioned, they found the average figures for the NaCl content of the c. s. fluid to be 741 and 715 mg per 100 cm<sup>3</sup> respectively.

If it is difficult to obtain correct information as to the chloride content of the c. s. fluid in healthy persons, it is still more difficult to obtain it about the relation between chlorides in the fluid and in the blood. Of the authors cited above, CSAKÍ (1924) states that the chloride content of the fluid is c. 25 % higher than in serum. LICKINT (1928) made c. 2,000 NaCl determinations in serum and found the normal values to vary between 570 and 630 mg per 100 cm<sup>3</sup>. As, according to his investigations, the NaCl content of the fluid is on an average 741 mg per 100 cm<sup>3</sup>, the relation between chlorides in fluid and serum would normally vary between 1.18 and 1.30. According to FREMONT-SMITH and co-workers (1931) the average figures for the NaCl content in the fluid is normally 725 per 100 cm<sup>3</sup> and in serum 592 mg per 100 cm<sup>3</sup>. Thus, according to these authors, the relation between chlorides in fluid and in serum is on an average 1.22. In WALTER's (1929) much quoted work on the blood-fluid barrier this relation is said to be 1.25.

HENDRY (1939) calculated the relation between the chloride content of fluid and blood (thus not serum) for his patients and found that it varied between 1.32 and 1.91, and averaged 1.59. As has been mentioned above, STEWART's (1928) statements on the normal chloride content of the fluid are, in my opinion, the most correct and, according to them, the NaCl content varies between 679 and 763 mg per 100 cm<sup>3</sup> and averages 715 mg per 100 cm<sup>3</sup> in children over 6 months of age. STEWART did not determine the NaCl in the blood. According to STRÖM (1935), in 35 children it varied between 489 and 554 mg per 100 cm<sup>3</sup> and averaged 524 mg per 100 cm<sup>3</sup>. The relation between the chloride content of the fluid (according to STEWART) and of the blood (according to STRÖM) thus averages 1.36. This method of calculating the relation thus gives a

considerably lower value than the one calculated with HENDRY'S figures.<sup>1</sup>

The index which we have arrived at cannot, of course, make any claims to a high degree of exactitude. The values are taken from different authors, who employed different methods. Consideration must also be paid to the fact that an index obtained by placing two average figures in relation to each other will not necessarily give the same result as that obtained by calculating the index for a number of individuals and taking the average figures for them. If there is a correlation between the values, a divergent results is obtained, and it is difficult to give any decided expression of opinion as to the significance of this source of error.

### The chloride content of the c. s. fluid, the blood-chloride and serum-chloride indexes in morbid conditions.

Opinions are divided as to the diagnostic value of the chloride content of the c. s. fluid. Many consider the examination of no great significance while others attach great importance to it. For instance, CsÁKI (1924) asserts that in meningitis cases it is of greater importance than determinations of the sugar; and, according to FOWWETTER (1930), a reduction in the chloride content of the fluid may be the first change in the fluid in a case of meningitis. As is shown below, studies of the literature afford definite support for the claim that in many cases the examination affords information which is of value for the diagnosis. In the Scandinavian countries, determinations of the chloride content of the c. s. fluid have attracted but little attention, and the only person, as far as I can find, who have occupied themselves with them are JACOBOWSKY (1929) at Uppsala and CHRISTIANSEN (1936) in Copenhagen.

#### *Tuberculous meningites.*

From a number of investigations it is known that the content of chlorides in the blood is reduced in tuberculosis, [BOENHEIM (1921),

<sup>1</sup> In what follows the relation between the chloride content in fluid and in whole blood, multiplied by 100, will be called the blood-chloride index, and the relation between chlorides in the fluid and in serum, multiplied by 100, the serum-chloride index.

BRIEGER (1925)], and the same condition was observed in the c. s. fluid at an early date (see Table 1). During the course of years this observation has been confirmed in different countries. In table 2 I have endeavoured to collocate the best investigations made during the last 20 years.

As the NaCl content of the c. s. fluid is normally c. 700 mg per 100 cm<sup>3</sup>, it appears from the table that all the authors found low values in tbc-meningitis, and the majority agree that no other disease causes such a great reduction as tbc-meningitis. Many have believed also that in this chloride content they had found a pathognomonic symptom of tbc-meningitis. The value the NaCl content must have, if it is to be a definite sign of tbc-meningitis, is 620 mg per 100 cm<sup>3</sup> according to MESTREZAT (1912), 600 mg per 100 cm<sup>3</sup>

Table 2.

*The NaCl content of the fluid in tuberculous meningites.*

Author	Year	Number of cases	NaCl in mg per 100 cm <sup>3</sup>
BROGSITTER and KRAUSS	1923	2	560, 810
NOWIKA	1924	60	510—680 average 595
CSÁKI	1924	9	454—642
MESTREZAT	1924	?	505—660
TUDÖS and EBEL	1927	4	620—670
LICKINT	1928	9	593—720
NEAL and ESSLEMONT	1928	25	500—720 average 613
SCHARAWSKY and MANDELBOIM	1929	4	490—620
STARY, KRAL and WINTERNITZ	1929	2	538—627
PRUNELL	1935	23	504—687
MARTIN, MACH and JUNET	1936	6	576—700
INGHAM	1937	84	420—550 average 510
HENDRY	1939	28	549—757

according to PRUNELL (1935), 590 mg per 100 cm<sup>3</sup> according to NOWICKA (1924), and 550 mg per 100 cm<sup>3</sup> according to INGHAM (1937). For purposes of comparison INGHAM examined 26 cases of non-tuberculous meningitis, and none of them had lower NaCl contents than 580 mg per 100 cm<sup>3</sup>. In contrast to this, LICKINT (1928) found that the NaCl content is no lower in tbc-meningitis than in epidemic meningitis, and that a normal content of NaCl in

the fluid does not exclude the possibility of a tbc-meningitis. HENDRY (1939) takes a similar view. These differing conceptions may possibly be due to the patients of the various authors having been examined in different stages of their illnesses.

As the tuberculous meningitis progresses, it is to be expected that NaCl in the fluid will decrease. CsÁKI (1924) examined 3 of his cases several times and found that the content of the NaCl fell from 589 to 577 mg per 100 cm<sup>3</sup> (in one day), from 642 to 558 mg per 100 cm<sup>3</sup> (in 5 days), and from 641 to 454 mg per 100 cm<sup>3</sup> (in 13 days). MESTREZAT (1924) also found that the curve for the chloride content falls gradually to the extremely low values during the course of the illness. In 5 of MARTIN, MACH and JUNET's (1936) 6 cases the chloride content of the fluid fell in the same way.

NEALE and ESSLEMONT (1928) and HENDRY (1939) arrived at a different conclusion. The first-named authors found that in 10 of their cases the chlorides in the fluid were low at first but definitely rose at the end of the illness, and in the majority of cases reached normal values (it is not stated what the conditions were in the authors' other 15 cases) HENDRY (1939) examined 22 of his cases at least twice and found that in 13 of them the chlorides in the fluid had increased.

At the same time as, or probably before (see below), the reduction of the chloride content of the fluid, a decrease in the chloride content of the blood also takes place. The content of NaCl in serum in tbc-meningitis is given by the following authors as: CsÁKI 481—505 mg per 100 cm<sup>3</sup>, PRUNELL 473—558 mg per 100 cm<sup>3</sup>. The content of NaCl in whole blood in tbc-meningitis cases was found by NEAL and ESSLEMONT to be 359—510 mg per 100 cm<sup>3</sup>, and by HENDRY (1939) 313—497 mg per 100 cm<sup>3</sup>. All the authors mentioned thus found that the chloride content of serum and blood is reduced in tbc-meningitis cases.

The above-mentioned so-called serum-chloride index and blood-chloride index indicate whether the reduction in c. s. fluid and serum and blood respectively takes place proportionately. In 2 cases STARY, KRAL and WINTERNITZ (1929) found the serum-chloride index to be 116 and 118 respectively, PRUNELL (1935) 109 and 116 and MARTIN, MACH and JUNET (1936) 112 and 131. NEAL



and ESSLEMONT (1928) found the blood-chloride index to be 129—159 and HENDRY (1939) 122—180.

*Summary:* In tbc-meningitis the chloride content is reduced in the c. s. fluid, and it is often lower than in any other illness. The chloride content is also clearly reduced in the blood. The serum-chloride and blood-chloride indexes therefore do not diverge from the normal. In certain cases the investigations which have been adduced are based on large materials, but the latter have not been subjected to detailed statistical analysis. It has been established in principle that changes are met with, but the detailed course and the variability have not been investigated.

*Bacterial meningites.*<sup>1</sup>

In bacterial meningitis cases the majority of authors have found a low chloride content in the c.s. fluid, though not so greatly reduced

Table 3.

*The NaCl content of the c.s. fluid in cases of bacterial meningitis.*

Author	Year	Bacteria	No. of cases	NaCl in mg per 100 cm <sup>3</sup>
MESTREZAT	1924	?	?	640—680
CSÁKI	1924	Meningococci	1	509—659
NOWICKA	1924	"	7	590—700 (average 656)
CAFFEY, MAC LEAN and SULLIVAN	1927	"	30	500—725
McMILLAN and RACE	1927	"	1	570—655
LICKINT	1928	"	19	608—757
"	"	Pneumococci	3	605—747
"	"	Streptococci	2	576—763
"	"	Staphylococci	2	680—689
"	"	Influenza bacilli	1	584
NEAL and ESSLEMONT	1928	Meningococci	6	615—706 (average 664)
"	"	Pneumococci	7	634—686 (average 664)
SCHARAWSKY and MANDELBOIM	1929	Meningococci	4	480—680
INGHAM	1937	?	26	580—690 (average 633)
HENDRY	1939	Meningococci	14	585—716

<sup>1</sup> By this will be understood in what follows all cases of meningitis in which bacteria have been established in the c. s. fluid, except tbc-meningitis cases.

as in tuberculous meningitis cases. NOWICKA (1924), NEAL and ESSLEMONT (1928) and INGHAM (1937) give the average figure for the NaCl content in the c. s. fluid in bacterial meningitis cases as 656 mg per 100 cm<sup>3</sup>, 664 mg per 100 cm<sup>3</sup> and 633 mg per 100 cm<sup>3</sup> respectively, while — as has been mentioned above — the same authors found the corresponding average figures for the meningitis cases to be 595 mg per 100 cm<sup>3</sup>, 613 mg per 100 cm<sup>3</sup> and 510 mg per 100 cm<sup>3</sup> respectively.

In table 3 I have given the NaCl content of the fluid according to a number of authors.

The range of the variation for the chloride content must naturally be large, as the fluid was examined in extremely varying stages of the illness.

The prognostic value of the chloride examination has been dealt with by many authors. CARREY and co-workers 1927 found that the NaCl content of the fluid in 24 cases of meningococcal meningitis which recovered before the treatment with serum had begun, averaged 644 mg per 100 cm<sup>3</sup>, while the average figure for the 6 patients who succumbed was only 629 mg per 100 cm<sup>3</sup>. They found, further, that the chlorides in the fluid rose gradually in the recovering patients, and that they reached the normal value c. 6 days after the beginning of the treatment. LICKINT (1928) mentions a fatal case in which the NaCl content gradually fell from 739 to 608 mg per 100 cm<sup>3</sup>, and another case, which recovered, where the NaCl content rose from 696 to 740 mg per 100 cm<sup>3</sup>. He gives a warning, however, against attaching too much importance to the investigation, as rises in cases with a favourable course and decreases in cases with an unfavourable course are by no means 100 per cent. He points out, however, that the investigation is of at least of as great importance as the sugar investigation, perhaps of greater importance. NEAL and ESSLEMONT (1928) describe a case of pneumococcal meningitis in which the chlorides in the fluid increased to normal values at the same time as the patient's condition improved greatly. After 9 days the patient disimproved rapidly, and the pathological findings in the fluid increased. The chloride content of the fluid decreased rapidly until the patient died. Two cases of meningococcal meningitis which recovered exhibited an increase of chlorides in the fluid, while they fell steadily in two fatal cases.

MCMILLAN and RACE (1927) made repeated lumbar punctures on a case of meningococcal meningitis which recovered. The number of cells decreased greatly, and the sugar index rose on the whole, while the chlorides in the fluid were approximately unchanged. Thus, no prognostic value can be ascribed to the investigation in this case.

The determination of blood-chloride and serum-chloride indexes in cases of bacterial meningitis has not attracted any great interest. In one case of meningococcal meningitis, NEAL and ESSLEMONT (1928) found that the decreases in the chloride content of the fluid and blood were approximately proportionate. HENDRY (1939) determined the blood-chloride index for 13 cases of meningococcal meningitis and found that it varied between 124 and 183 and averaged 149. In normal cases this author found that the blood-chloride index varied between 132 and 191 and averaged 159. HENDRY's investigation might possibly indicate that the chlorides decrease more in the c. s. fluid than in the blood in cases of meningococcal meningitis. The index determinations will hardly be of any great diagnostic or prognostic value.

In the literature there is no evidence that certain bacteria give rise to an especially low chloride content in the c. s. fluid (see table 3).

*Summary:* In cases of bacterial meningitis the chloride content is reduced in the c. s. fluid. Its determination has a certain diagnostic value. Blood-chloride and serum-chloride indexes will have no definite value. There is no evidence that certain bacteria give rise to a lower chloride content in the fluid than others.

#### *Aseptic purulent meningites.*

These meningitis cases often have unknown etiologies and usually have a benign course and exhibit pleocytosis, increased albumin and normal sugar content in the c. s. fluid. The chloride content of the fluid in CSÁKI's (1924) two cases was 680 and 674 mg per 100 cm<sup>3</sup>. SCHARAWSKY and MANDELBOIM (1929) mention 8 cases, of which four had normal and four reduced (630—680 mg per 100 cm<sup>3</sup>) NaCl contents in the fluid.

#### *Poliomyelites.*

In cases of this disease FREMONT-SMITH and AYER (1927) and LICKINT (1928) found normal or slightly reduced chloride content in the fluid. In the last-mentioned author's 11 cases the values varied between 688—781 mg per 100 cm<sup>3</sup> and averaged 730 mg per 100 cm<sup>3</sup>.

According to TÖRÖK (1933, 16 cases) the NaCl content may be somewhat reduced, normal or even somewhat increased, in the pre-paralytic stages of the illness. A number of authors mention isolated cases, of whom the majority have a chloride content lying within the normal limits.

*Tumours in the central nervous system.*

The following authors state that, in cases of cerebral tumours, the chloride content of the c. s. fluid is normal: BROGSITTER and KRAUSS (1923, 2 cases), CSÁKI (1924, 1 case), NEAL and ESSLEMONT (1928, 9 cases), STARY, KRAL and WINTERITZ (1929, 2 cases). Of LICKINT's 8 cases 2 had reduced, 5 normal and 1 increased chloride contents, and of SCHARAWSKY and MANDELBOIM's 9 cases 5 had reduced and the other 4 normal chloride contents in the fluid. CHRISTIANSEN (1936) has a material of 13 cerebral tumours, in which the ventricles were punctured. The NaCl content of the ventricle fluid varied between 681 and 747 mg per 100 cm<sup>3</sup> and averaged 734 mg per 100 cm<sup>3</sup>. The normal value for the ventricle fluid is not known, but it will probably lie between the extreme limits here given by CHRISTIANSEN.

The chloride content of the c. s. fluid will therefore be of no assistance for the diagnosis of cerebral tumours.

*Other diseases in the central and peripheral nervous systems.*

*Epilepsy:* The chloride content of the c. s. fluid has in general been found to be normal, and is 715—727 mg per 100 cm<sup>3</sup> according to CSÁKI (1924, 2 cases of Jacksonian epilepsy), 714—738 mg per 100 m<sup>3</sup> according to FREMONT-SMITH and DAILEY (1925, 11 cases), 684—743 mg per 100 cm<sup>3</sup> according to HAMILTON (1925, 16 cases), 709—790 mg per 100 cm<sup>3</sup> according to LICKINT (1928, 10 cases, of which 2 were considered to have somewhat increased and the others normal chloride contents), 725—769 mg per 100 cm<sup>3</sup> according to NEAL and ESSLEMONT (1928, 2 cases), 700—730 mg per 100 cm<sup>3</sup> according to SCHARAWSKY and MANDELBOIM (1929, 3 cases). The only investigator, as far as I can find, who determined the chloride content of the fluid during attacks is HAMILTON (1925), who performed lumbar punctures on 2 patients, one during an attack of petit mal, the other in immediate association with a general attack of convulsions. In neither of these 2 cases did the chloride content of the fluid differ from those of the other epilepsy patients.

The series of cases or isolated cases of *sclerose en plaque*, *lues in the central nervous system*, *amyotrophic lateral sclerosis*, *bulbar paralysis*, *ataxia*, etc., more or less unusual nervous diseases, show a normal chloride content in the c. s. fluid, although inconsiderable divergencies both upwards and downwards are met with. BROGSITTER and KRAUSS (1923), CSÁKI (1924); NIINA (1925), REGAN and GUINNESS (1927), LICKINT (1928), SCHARAWSKY and MANDELBOIM (1929), STARY, KRAL and WINTERNITZ (1929), FREMONT-SMITH and co-workers (1931).

STARY and co-workers (1929) mention 9 cases of *dementia praecox* which had an average chloride content of 731 mg per 100 cm<sup>3</sup> in the fluid.

LICKINT states that in 8 cases of *commotio cerebri* 2 had somewhat increased and others normal chloride contents in the fluid. According to FREMONT-SMITH and co-workers, one case of fracture of the skull with hemorrhage had 660 mg per 100 cm<sup>3</sup> NaCl in the fluid, and the NaCl content in 2 cases of subarachnoidal hemorrhage was 713 and 723 mg per 100 cm<sup>3</sup> respectively. Intracranial hemorrhages can thus give rise to a reduced chloride content of the fluid.

#### *Renal diseases.*

There has been considerable discussion as to whether the general retention of chlorides which may be met with in kidney diseases reveals itself in the form of a reduced or increased NaCl content of the c. s. fluid. According to MESTREZAT (1924) in uraemia and similar conditions it varies between 750 and 900 mg per 100 cm<sup>3</sup>. NEUDA (1923) also found a high chloride content in the fluid in uraemia, but on the other hand a low content in chronic nephritis. CSÁKI's (1924) 4 cases of nephritis had a NaCl content of 708—813 mg per 100 cm<sup>3</sup>. LICKINT (1928) gives 10 cases of nephritis without uraemia in which the NaCl in the fluid varied between 694 and 816 mg per 100 cm<sup>3</sup> (1 case low, 1 case at the lower and 4 cases at the upper limit for the normal; 4 cases clearly increased). In 25 cases of uraemia the NaCl content of the blood was 554—944 mg per 100 cm<sup>3</sup> (5 cases low, 10 cases normal, 10 cases obviously increased). 7 cases of eclampsia had a NaCl content of the fluid varying between 717—792 mg per 100 cm<sup>3</sup> (6 normal and 1 increased). Among FREMONT-SMITH and co-workers (1931) 10 cases of chronic kidney disease, the chloride content was low in 1 case, normal in 7 cases, and

somewhat increased in 2 cases; and of 5 cases of uraemia 1 had low, 2 normal and 2 increased chloride contents in the fluid.

Thus in chronic kidney diseases the chloride content of the fluid may be either low, normal or increased.

### The sugar content of the fluid and the sugar index in normal and morbid conditions.<sup>1</sup>

The sugar content of the c. s. fluid is higher in cistern than in lumbar fluid. This difference is very inappreciable, however, and will probably be of no practical significance. In the ventricle fluid the sugar content is considerably higher than in the cistern and lumbar fluids (FREMONT-SMITH and AYER 1927, STEWART 1928, SAMSON 1931). During the first 6 months of life the sugar content is in general higher than during the remainder of life. During the second 6 months of life the sugar content varies a great deal, but remains on approximately the same level as in older children and adults (SAMSON 1931).

The normal sugar content of the c. s. fluid varies a great deal, and a table is given below showing this, according to different authors. The table is taken from SAMSON's (1931) work.

Table 4.  
*The normal sugar content of the c. s. fluid.*

Author	Border-line values	Average
BLUM	48—63	56
V. BOKAY	55—80	—
BRUCKE	—	56
CHEVASSUT	100—150	—
	80—93	—
LAGERGREN	38—90	61
LEVINSON	46—75	—
SAENGER	50—75	—
STEINER	55—70	—
STEVENSON	50—70	—
STEWART	27—84	—
TRENDTEL	50—70	—

<sup>1</sup> This wide field within the chemistry of the c. s. fluid is dealt with very briefly here. For more detailed studies reference should be made to MUNCH-PETERSEN (1929) and SAMSON (1931).

Narrower limits for the normal sugar in the c. s. fluid 41—60 mg per 100 cm<sup>3</sup> are given by CsÁKI (1924), 50—75 mg per 100 cm<sup>3</sup> by FREMONT-SMITH and AYER (1927), and ESKUCHEN (1927) 45—65 mg per 100 cm<sup>3</sup> by NISSEN (1927), 45—83 mg per 100 cm<sup>3</sup> by NEAL and ESSLEMONT (1928), 50—53 mg per 100 cm<sup>3</sup> by SCHARAWSKY and MANDELBOIM (1929).

As the sugar in the fluid is very dependent on the sugar in the blood, and under normal conditions widely seen runs parallel to it, the sugar index ( $= \frac{\text{the sugar content in fluid}}{\text{the sugar content in blood}} \times 100$ ) is of greater interest than the sugar content of the fluid. The sugar index, under

Table 5.  
*The normal sugar index.*

Author	Index
DERRIEN	50—
WITTGENSTEIN	54—58
DIDE, FAUGES and BAUDUIN	45—63
GOODWIN and SHELLY	45—65
BLUM	52—60
POLONOWSKI and DUBOT	45—85
WEICHMANN	54—68
HALLIDAY	50—70
NIXON and SEHAM	48—70
FORTI	50

normal conditions, according to various authors, is shown in the table, which is taken from MUNCH-PETERSEN's (1929) work.

Reduced sugar in the c. s. fluid and a reduced sugar index is of great diagnostic value. It is met with above all in acute purulent meningitis and in the-meningitis. A normal or high sugar value and sugar index are stated to be met with in encephalitis, cerebral tumours, cerebral hemorrhage, poliomyelitis, convulsions, nephritis and, naturally, diabetes mellitus. [ESKUCHEN (1919), MESTREZAT (1924), CsÁKI (1924), FOSTER and COCKRELL (1924), NIINA (1925), WILCOX and LYTLE (1925), FREMONT-SMITH and AYER (1927), NEAL and ESSLEMONT (1928), STEWART (1928), SCHARAWSKY and MANDELBOIM (1929), LICHTENSTEIN (1932), BERGMAN (1935), NISSEN (1936), BECKER (1939)].

## THE AUTHOR'S OWN INVESTIGATIONS.

### Material.

It has been mentioned in the preface that the specimens of c. s. fluid for the present investigation were obtained from a number of different kinds of hospitals in Stockholm (children's hospitals, one epidemic hospital, a hospital for adults with medical diseases, a neurological and a neurosurgical clinic, and a home for epileptics).

The whole material comprises 428 cerebrospinal fluids from 355 patients. Of these 33 were very slightly ill, or suffering from some illness which, according to what there is reason to suppose, had not given rise to any morbid changes in the fluid (see below). These 33 cases are designated as normal cases below.

According to what has been pointed out above in the survey of the literature (p. 13), the fluid in children under 6 months differs in several respects from that in older children and adults. As no material from normal cases could be obtained from children in the first 6 months of life, and as, further the pathological cases in this age-group are somewhat few in number, such are not included in the investigation. The number of cerebrospinal fluids examined from children between the ages of 6 months and 15 years is 252 (from 189 children). The other 176 cerebrospinal fluids were taken from 166 patients above 15 years of age, the oldest patient being 56 years of age.

The lumbar, cistern and ventricle punctures were made independently of the time of day, meals, supplies of medicine, etc.

### Methods.

The needles used for the lumbar, cistern and ventricle punctures were boiled in sterile water or dry-sterilized in an autoclave.

When the puncture was made, the first few drops to issue were



not collected. The first part of the fluid which followed was used for Cl-ion determinations, and the last part for the other investigations.

*The Cl-ion determinations.* The fluid was kept in centrifuge tubes holding 10 ml., closed with rubber corks, and stood in a refrigerator for not more than two weeks, and seldom for more than 1 week before the Cl-ion determination was made.<sup>1</sup> This was done by electro-metric microtitration according to E. MÜLLER (1926).<sup>2</sup> One electrode was a silver plate c. 0.25 cm<sup>3</sup> in size, which was rotated by means of an electric motor, and thus was at the same time the mixer. The other electrode was a calomel electrode with Hg<sub>2</sub>Cl<sub>2</sub> in saturated KCl-solution, and in connection with it a u-tube filled with saturated KNO<sub>3</sub> in 4 % agar. The last-mentioned tube was thus immersed into the fluid which was to be examined. The change in potential was determined each time the calomel electrode was changed and sometimes controlled in between. The potentials varied between 274 and 300 millivolts, and the potentiometre was set at the determined potential before the beginning of the titration. The latter was carried out with 0.005 normal AgNO<sub>3</sub>. As a control for this titre a 0.1000 normal NaCl solution (obtained by the solution of 5,846 g of dry NaCl in 1000 ml of water) was used. This initial titre solution was kept in bottles of Jena glass with ground glass stoppers. A burette with automatic zero-point setting calibrated to 0.05 ml and capable of being read off to 0.01 ml was used for the AgNO<sub>3</sub>-solution.

For the titration 0.1 ml of the c. s. fluid was drawn up into a micropipette of the design used in determinations of blood-sugar according to Hagedorn-Jensen, and then ejected into a glass beaker containing 2 ml of 15% trichloroacetic acid. 3—4 ml of distilled water was added, after which this solution was placed in contact with the electrodes, and so much of the AgNO<sub>3</sub> solution added that the indicator of the potentiometer pointed to 0.

For Cl-ion determinations in capillary blood 0.1 ml of blood

<sup>1</sup> In about 20 cases the determinations were made, firstly, immediately after the puncture, and secondly, a second time after the fluid had been kept in this way for 2 weeks. The values were found to be the same, so that this conservation could not have played any rôle as regards the Cl-ion content.

<sup>2</sup> The potentiometre from Cambridge Instrument Comp. Catalogue no. 442/1933.

was drawn up into a micro-pipette of the above-mentioned design and ejected into a centrifuge tube containing 1.9 ml. of distilled water, so that complete hemolysis was secured. The pipette was rinsed several times with this hemolysate. The tubes, well closed with rubber corks, were kept in a refrigerator for one week, rarely up to 2 weeks. For Cl-ion determinations, 2 ml of 15 % trichloroacetic acid was added, and after the tubes had stood for about 5 minutes the precipitation was centrifuged. 3 ml of the clear centrifugate was pipetted off and titrated with  $\text{AgNO}_3$  in the same way as in the case of the fluid.

*Sugar determinations* were made according to Hagedorn-Jensen's methods on 0.1 ml of blood and fluid. The blood specimens were taken immediately before the lumbar and cistern punctures.

*Other examinations of the c. s. fluid.* Cell counts were made in accordance with Fuchs-Rosenthal's method, except in some cases where the cell counts were made in a Bürker's chamber. The fluid of all the normal cases was examined in accordance with Fuchs-Rosenthal. The albumin investigations were according to Nonne and Pandey, and the mastix reaction were carried out according to current clinical methods of examination.

The bacteriological examinations were made at the Bacteriological Laboratory of the Board of Health in Stockholm.

The examinations of the Cl-ion content of the c. s. fluid and of blood were made by the present author himself, except in a small number of cases. The other examinations were made at the laboratories of the respective hospitals.

*Statistical methods:* In the statistical working up of the material the current formulas were used. The standard deviation,  $\sigma$ , was thus calculated from the formula:

$$\sigma = \pm \sqrt{\frac{\sum a^2}{n-1}}$$

where  $a$  = deviations from the mean figure and  $n$  = the number of determinations.

The standard error of an average figure,  $\epsilon (M)$  was calculated from the formula:

$$\epsilon (M) = \pm \frac{\sigma}{\sqrt{n}}$$

As a rule the computations were made on at least 15 values. For a smaller number of values a special correction was made. The standard error was multiplied by  $\sqrt{\frac{N-n}{n}}$ , where  $N$  is the total number of both groups which are being compared,  $n$  the number of one of the groups.

A difference was considered statistically significant when it exceeded 3 times the mean error. If it amounted to  $2\frac{1}{2}$  times, but not to 3 times, the standard error, the difference was considered to be probable. If the difference was less than the standard error, the correspondence was considered good, and in other cases it was considered satisfactory.

In calculating the standard error of the methods, double determinations were made.  $\sigma_2$ , the standard error of the individual determinations, is obtained from the formula:

$$\sigma_2 = \pm \sqrt{\frac{\sum d^2}{2n}}$$

where  $d$  = differences between double values (DAHLBERG 1926).

An orientation of the standard error of the methods is obtained from table 6.

Table 6.

	No. of double determinations	Standard error of a single determination as %
Cl-ion content of the fluid .....	557	0.49
Blood chlorides .....	484	1.96
Sugar content of the fluid .....	230	5.52
Blood sugar .....	216	6.09

Further, the reliability of the pipettes used for the determinations was investigated. The results appear in table 7.

Pipettes 0 and 00 are manufactured with special accuracy, and their capacity has been controlled at the Chemical Institution of the Caroline Institute by the weighing method. It appears that the average values obtained with different pipettes are in good agree-

Table 7.

Control of 21 pipettes by means of 15 titrations with each pipette.

Pipette no.	$M \pm \epsilon (M)$	$\sigma$	$\sigma$ 2.15	$\sigma$ 2.15 as % of 2.15
0	$2.150 \pm 0.0034$	0.0131	0.0131	0.61
00	$2.149 \pm 0.0036$	0.0139	0.0139	0.65
1	$2.149 \pm 0.0049$	0.0188	0.0189	0.88
2	$2.148 \pm 0.0033$	0.0126	0.0128	0.60
3	$2.153 \pm 0.0034$	0.0133	0.0136	0.63
4	$2.151 \pm 0.0034$	0.0133	0.0134	0.62
5	$2.149 \pm 0.0032$	0.0125	0.0125	0.58
6	$2.149 \pm 0.0032$	0.0125	0.0125	0.58
7	$2.151 \pm 0.0042$	0.0164	0.0165	0.77
8	$2.154 \pm 0.0034$	0.0130	0.0136	0.63
9	$2.152 \pm 0.0030$	0.0115	0.0116	0.54
10	$2.151 \pm 0.0035$	0.0136	0.0136	0.63
11	$2.151 \pm 0.0030$	0.0116	0.0116	0.54
12	$2.150 \pm 0.0040$	0.0156	0.0156	0.73
13	$2.153 \pm 0.0040$	0.0153	0.0156	0.73
14	$2.152 \pm 0.0022$	0.0086	0.0089	0.41
15	$2.150 \pm 0.0032$	0.0125	0.0125	0.58
16	$2.153 \pm 0.0032$	0.0123	0.0128	0.60
17	$2.154 \pm 0.0025$	0.0099	0.0107	0.50
18	$2.154 \pm 0.0035$	0.0135	0.0141	0.66
19	$2.151 \pm 0.0038$	0.0149	0.0149	0.69
20	$2.153 \pm 0.0035$	0.0135	0.0139	0.65
21	$2.151 \pm 0.0025$	0.0096	0.0096	0.45

ment which the values of the controlled pipettes, and that the variability which characterises the specimen-taking with pipettes remains about  $\frac{1}{2}$  % on the whole.

The Cl-ion and sugar contents of the c. s. fluid and the blood-chloride and sugar indexes in the normal condition.

As it is not considered expedient to perform lumbar punctures on quite healthy persons, in view of the discomfort and the risk (small though it is), in this work lumbar punctures were not made

on perfectly healthy persons. Instead of such healthy material, certain clinical cases were selected, in which there was reason to suppose that the content of chlorides and sugar in the fluid and blood were as large as in healthy persons. This material is called normal material. It consists of 33 patients, of whom 20 were under and 13 over 15 years of age. The youngest was 1 <sup>11</sup>/<sub>12</sub> and the oldest 31 years old. The diagnoses were very varied, such as neuropathia, psychopathia, pharyngitis ac., lymphadenitis colli, rubeola, etc. None of the patients could be classified as suffering from organic nervous diseases, nor did any of them exhibit symptoms of luetic<sup>1</sup> or tuberculous diseases. The following were common to them all: neurological status (physical strength, reflexes, pupils, Babinski) were normal (the majority were a little stiff in the neck, which was the indication for the lumbar or cistern puncture). The c. s. fluid had a normal pressure (up to 20 cm), a normal number of cells (a maximum of 8/3 per mm<sup>3</sup>, the majority 0 cells). Nonne neg. and Pandy neg. or slightly pos.

In the examination of the normal material, a group of clearly normal cases (26 cases) was separated from a group of more doubtful cases (7 cases). In a comparison between the results of the examination as regards Cl-ions etc., the group of doubtful cases proved to lie well inside the variation range for the normal. These groups were thrown together in order to increase the material. This was done the more readily as this procedure implies — if the doubtful group deviates — that the variability increases, and the mean error calculated rather becomes somewhat larger. There is hardly any reason not to throw the material together under such circumstances.

It is shown below that the Cl-ion content of the fluid and the blood-chloride index are independent of whether the fluid is obtained by means of lumbar or cistern puncture. The sugar content will probably not be exactly as large in lumbar as in cistern fluids (see above in the survey of the literature). The difference is inconsiderable, however, and the normal variations are large.<sup>2</sup> The values for cistern and lumbar fluids have therefore been added together in the normal material. It may be pointed out that, to

<sup>1</sup> Wassermann's test was applied to the majority of cerebrospinal fluids and found to be negative.

<sup>2</sup> If the epilepsy cases are excluded, cistern punctures were made only in a few cases in the whole material.

Table 8.  
Normal material.

	Lumbar fluid			Cistern fluid		Total		
	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	No.	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid.....	27	122.85 $\pm$ 0.39	2.03	6	124.15	33	123.09 $\pm$ 0.35	2.02
Blood-chloride index.....	27	141.11 $\pm$ 1.29	6.69	6	143.17	33	141.48 $\pm$ 1.12	6.41
Sugar content of the fluid.....	25	66.00 $\pm$ 2.15	10.73	5	61.60	30	65.27 $\pm$ 1.90	10.39
Sugar index .....	25	63.36 $\pm$ 2.08	10.42	5	66.00	30	63.80 $\pm$ 1.83	10.01

the extent that any isolated case with pathological changes should happen to be included in the normal, this leads to an increase in the range of the variation. If it is only a matter of one or two cases, however, such a possible increase is most likely to be of no importance.

The results of the investigation of the normal material are shown in table 8.

It appears from the table that in healthy or slightly affected patients, who are not suffering from diseases in the central nervous system, and in whose fluids no morbid changes have been proved, the Cl-ion content of the fluid is  $123.09 \pm 0.35$  mmol. ( $= 720.1 \pm 2.05$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $141.48 \pm 1.12$ , the sugar content of the fluid  $65.27 \pm 1.90$  mg per 100 cm<sup>3</sup>, and the sugar index  $63.80 \pm 1.83$ .

The range of variation for the Cl-ion content of the fluid extends from 118.7 mmol ( $= 694.4$  mg NaCl pr 100 cm<sup>3</sup>) to 126.8 mmol ( $= 741.8$  mg NaCl pr 100 cm<sup>3</sup>), for the blood-chloride index from 128 to 156, for the sugar content of the fluid from 48 to 89 mg pr 100 cm<sup>3</sup> and for the sugar index from 50 to 81.

As regards the chloride content, the results agree extremely well with STEWART'S (1928) results, which in my opinion — as has been mentioned above — are the most reliable. He found the NaCl content of the fluid in children 6 months — 12 years of age to vary between 679 and 763 mg per 100 cm<sup>3</sup> and the mean to be 715 mg per 100 cm<sup>3</sup>. The blood-chloride index calculated according to STEWART'S (1928, fluid) and STRÖM'S (1925, blood) results averaged 136 and thus agrees fairly well with the values found in the present

Table 9.

*The significance of vomiting for the Cl-ion content of the c.s. fluid and blood.*

	Patients who have vomited during the last 24 hours.			Patients who have not vomited during the last 24 hours.			Cases where there is no information about vomiting		
	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid	16	122.66 $\pm$ 0.64	2.56	33	124.00 $\pm$ 0.50	2.84	37	124.46 $\pm$ 0.45	2.74
Cl-ion content of the blood	16	84.81 $\pm$ 1.31	5.24	32	86.93 $\pm$ 0.68	3.84	37	85.89 $\pm$ 0.78	4.76
Blood-chloride index.....	16	145.06 $\pm$ 2.09	8.37	32	142.72 $\pm$ 1.13	6.39	37	145.49 $\pm$ 1.23	7.48

work. Although the range of variation of the sugar content and the sugar index is great in my material, the values agree on the whole with the results of previous investigators (see tables 4 and 5).

Some circumstances who may influence the content of chlorides in the c. s. fluid.

*The significance of vomiting for the Cl-ion content of the c. s. fluid and for the blood-chloride index.*

To what extent the organisms supply and loss of NaCl affect the Cl-ion content of the fluid is very difficult to ascertain and, as has been mentioned above, there is but little information in the literature on the subject. I have only taken up one detail of this problem for examination, namely, the importance of vomiting in this respect.

A relatively large number of the cerebrospinal fluids with normal Cl-ion contents examined derive from poliomyelitis material (see p. 54). This has been divided into three groups, namely, 1) patients who vomited once or several times during the 24 hours before the puncture, 2) patients who did not vomit during that period, and 3) patients about whom it is not known whether they vomited or not. The state of things as regards the Cl-ion content of the fluid and of the blood-chloride index in these groups appears from table 9.

The difference for the Cl-ion content of the fluids between group

2 and 1 is  $1.34 \pm 0.81$  mmol., and that for the blood-chloride index  $2.34 \pm 2.38$ , and neither of them is significant.

Thus, in patients suffering from poliomyelitis the vomitings are of no definite importance for the Cl-ion content of the fluid or for the blood-chloride index. As the vomiting of the poliomyelitis patients was inconsiderable, the question must be left open as to the extent to which heavy vomitings affect the conditions mentioned.

*Is there any difference between the Cl-ion content in lumbar and in cistern fluids?*

To find an answer to this question, it is best to examine the fluids obtained by simultaneous lumbar puncture and puncture of the Cisterna magna in patients with a free passage for the fluid. This examination was carried out on 6 patients suffering from different nervous diseases and with a normal Cl-ion content of the fluid. (It was difficult to obtain a larger material). The average Cl-ion content of the lumbar fluid was 122.63 mmol., and of the cistern fluid 123.72 mmol, the difference being 1.08. Owing to the paucity of the material, this examination affords no evidence as to whether there is any difference in the respect mentioned or not.

Another method of throwing light on this question is to examine the Cl-ion content of different portions of the lumbar fluid in a fractional lumbar puncture. In 19 children the fluid first obtained was kept for investigation, after which 15—20 ml of the fluid was drawn off, and the fluid which then flowed out was kept for Cl-ion determinations. The subarachnoid space of the spinal column in adults contains 60—80 ml of fluid (according to ESKUCHEN 1919 c. 60 ml, according to WEIGELDT 1936 an average of 77 ml), and the capacity in children is naturally smaller. The ages of the children in the present material were 3 years and upwards, and the fluid in the last portion drawn off probably came from the Cisterna magna, or from the upper part of the subarachnoid space in the spinal column.

Table 10.

*The Cl-ion content of the c. s. the fluid in fractional lumbar punctures.*

	No.	$M \pm \epsilon (M)$	$\sigma$
Portion 1 . . . . .	19	$124.25 \pm 0.62$	2.71
• 2. . . . .	19	$124.25 \pm 0.64$	2.81
Diff. . . . .	—	$+0.005 \pm 1.09$	1.09



Table 11.

*The Cl-ion content of lumbar and cistern fluids.*

	Lumbar fluid			Cistern fluid			Diff.
	No.	$M \pm \epsilon (M)$	$\sigma$	No.	$M \pm \epsilon (M)$	$\sigma$	$D \pm \epsilon (D)$
Cl-ion content of the fluid . . . .	24	$123.89 \pm 0.60$	2.94	30	$123.73 \pm 0.39$	2.12	$0.16 \pm 0.72$
Blood-chloride index . . . . .	24	$140.08 \pm 1.05$	5.16	28	$141.71 \pm 1.64$	8.67	$1.63 \pm 1.95$

The table shows that in fractional lumbar punctures the Cl-ion content in the first portion of the fluid is as great as in the last portion.

A third method of investigating whether there is any difference in the Cl-ion content of the lumbar and cistern fluids, is to take a group of healthy persons, or a group of patients suffering from some disease who show no, or only inappreciable changes in the fluid, and compare the Cl-ion content of the fluid of those who have had lumbar punctures with the Cl-ion content of the fluid of those who have had cistern punctures. The fluid from 54 epilepsy patients provides a suitable material for such an investigation.

It appears from table 11 that in epilepsy patients there is no difference between the Cl-ion content of the lumbar and cistern fluids.

Three different ways of calculating whether the content of Cl-ions is the same in lumbar and cistern fluid have been given above. None of these calculations by itself justifies any general conclusions, but as the results all point to the same direction, it will probably be verified that there is no difference in the Cl-ion content of the lumbar and the cistern fluids.

This conclusion thus confirms STEWART's (1928) results, but is in conflict with the findings of other investigators. (MALYKIN, 1930, LEIPOLD, 1935).

#### *Age and the Cl-ion content of the c. s. fluid.*

It was mentioned in the survey of the literature, that there is no reason to suppose that the Cl-ion content of the fluid is dependent on age (except during the first 6 months of life). To decide what the conditions are in this respect, the poliomyelitis material was used.

Table 12.

*Changes in the Cl-ion content at increasing ages.*

Age	Cl-ion content of the fluid		Blood-chloride index	
	No. of cases	Average	No. of cases	Average
1—5	9	123.68	9	1.41
6—10	19	124.36	19	1.44
11—15	12	125.28	11	1.44
16—20	6	123.83	6	1.52
21—25	10	124.71	9	1.47
26—30	7	122.43	7	1.41
31—W	14	124.61	14	1.46
1—10	28	$124.14 \pm 0.47$	28	$1.43 \pm 0.014$
11—20	18	$124.79 \pm 0.61$	17	$1.47 \pm 0.015$
21—W	31	$124.15 \pm 0.52$	30	$1.45 \pm 0.014$

Correlation between age and the Cl-ion content of the fluid =  $+ 0.04 \pm 0.11$   
 , , , , , blood-chloride index =  $+ 0.18 \pm 0.11$

It comprised 77 patients, the youngest 1 year and 2 months and the oldest 56 years of age. The Cl-ion content of the fluid of these patients lies within the normal limits. (see below p. 56).

It emerges from table 12 that, in a considerable material of poliomyelitis patients, *there is no correlation between age and the Cl-ion content of the fluid, nor between age and the blood-chloride index.* This result thus tallies with STEWART'S (1928).

The Cl-ion and sugar contents of the c. s. fluid and the blood-chloride and sugar indexes in morbid conditions.

#### Tuberculous meningitis.

The material comprises 35 lumbar fluids from 16 patients. The majority died of miliary tuberculosis. In all the cases the diagnosis tbc-meningitis was verified, either by the finding of tubercle bacilli in the fluid or by autopsy.

The result of the investigation is shown in table 13.

As will be seen, the material was divided into 2 groups, namely, cerebrospinal fluids which were obtained by punctures during the

Table 13.  
*Tuberculous meningites.*

	8—18 days before death			1—7 days before death			Total cases		
	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid .....	15	109.96 $\pm$ 2.47	$\pm$ 9.56	20	102.89 $\pm$ 1.67	$\pm$ 7.45	35	105.92 $\pm$ 1.52	$\pm$ 9.01
Blood-chloride index	15	133.93 $\pm$ 2.32	$\pm$ 8.98	20	131.00 $\pm$ 2.33	$\pm$ 10.43	35	132.26 $\pm$ 1.66	$\pm$ 9.81
Sugar content of the fluid .....	14	34.43 $\pm$ 3.45	$\pm$ 12.92	20	27.65 $\pm$ 3.00	$\pm$ 13.42	34	30.44 $\pm$ 2.31	$\pm$ 13.45
Sugar index .....	14	31.73 $\pm$ 4.99	$\pm$ 19.34	18	19.61 $\pm$ 1.89	$\pm$ 8.00	34	25.12 $\pm$ 2.67	$\pm$ 15.34

earlier stages of the illness, and such as were obtained by punctures during the week before death. The greatest interest attaches to the average figures for all the cases of tbc-meningitis, which are given in the last main part of the table.

The average figure for the Cl-ion content of the fluid is 619.63  $\pm$  8.89 mg NaCl per 100 cm<sup>3</sup> and lies within the extremely wide limits given by earlier authors (see table 2).

It appears from table 13 that the mean values are very low, and the difference between the normal material and all the tbc-meningitis cases is 17.17  $\pm$  1.56 mmol for the Cl-ion content of the fluid, 9.22  $\pm$  2.00 for the blood-chloride index, 34.83  $\pm$  2.99 mg per 100 cm<sup>3</sup> for the sugar in the fluid, and 38.68  $\pm$  3.24 for the sugar index. All these differences are significant.

As appears from table 13, the average figures for the group of patients who were examined during the week before death are lower than for the group which was examined earlier. The differences between the average figures are 7.07  $\pm$  2.98 mmol for the Cl-ion content of the fluid, 2.93  $\pm$  3.29 for the blood-chloride index, 6.78  $\pm$  4.57 mg per 100 cm<sup>3</sup> for the sugar content of the fluid, and 12.12  $\pm$  5.34 for the sugar index. None of these differences is significant, and thus it is not proved that the values for the conditions examined here fall during the course of the illness. Another method for trying to discover the state of things in this respect is simply to investigate the conditions in the individual case. For the sake of surveyability this has been done graphically.

Fig. 1 shows the state of things as regards the Cl-ion content of

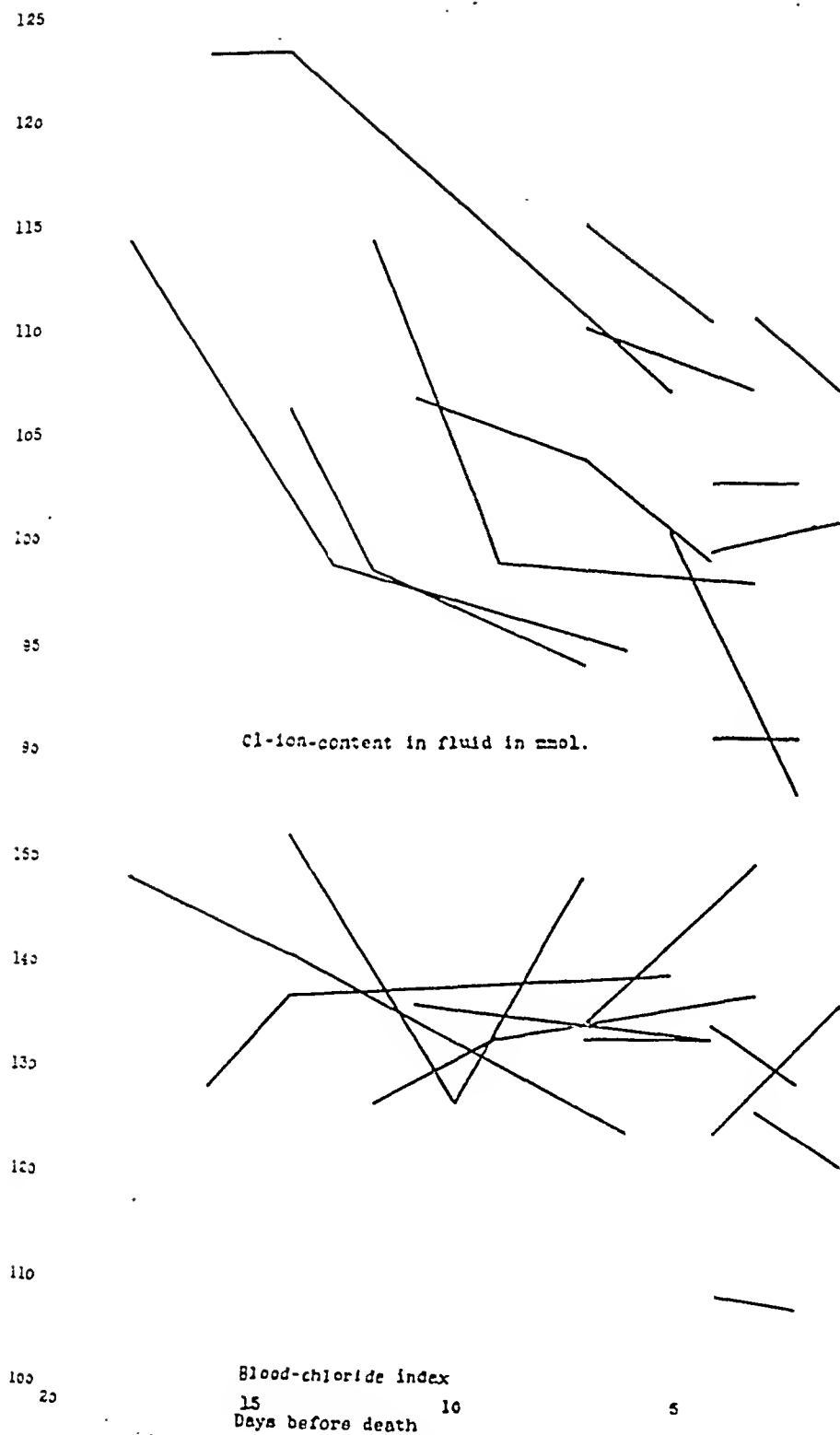


Fig. 1.

the fluid and of the blood-chloride index during the course of the illness in the 12 and 11 cases respectively which were examined at least twice.

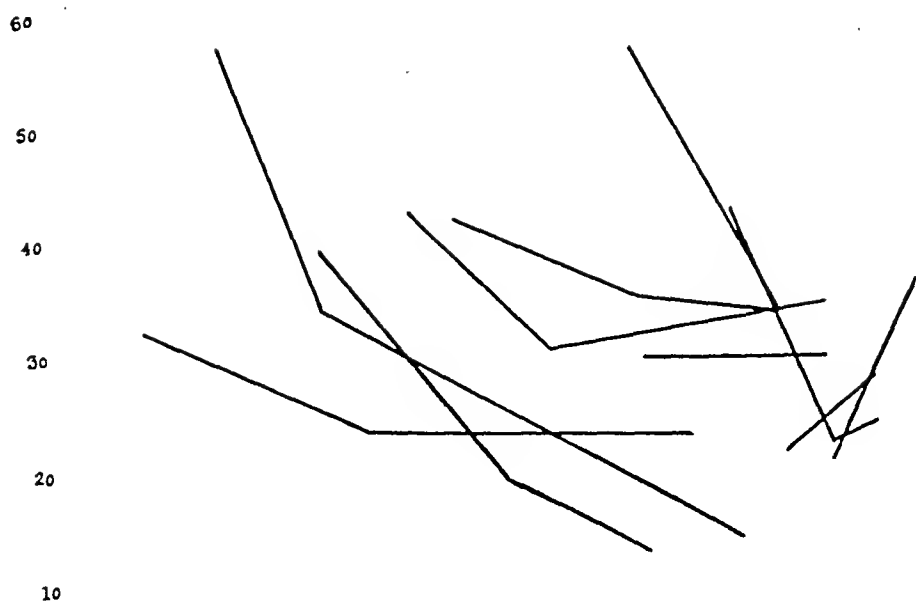
In the figure it appears that the Cl-ion content of the fluid fell, in all the cases but one, in which it rose inappreciably, and in 2 cases, where it remained the same. The 3 cases lastmentioned were, however, punctured during the last stage of the illness and had greatly reduced Cl-ion contents already at the time of the first puncture. The investigations confirm CsÁKI's (1924) and MARTIN, MACH and JUNET's (1936) results, but run contrary to the investigations of NEAL and ESSLEMONT (1928) and HENDRY (1939). Further, the figure shows that in 6 of the 11 cases the blood-chloride index fell during the course of the illness, in 4 cases it rose, and in 1 case it first fell and then rose.

The difference between the average figure for the Cl-ion content of the fluid in the group »8—18 days before death» and in the group »1—7 days before death» is, as is stated above,  $7.07 \pm 2.98$  mmol (the difference is thus c. 2.4 times larger than the standard error of the average) and the corresponding difference for the blood-chloride index is  $2.93 \pm 3.29$  (the difference is thus less than the standard error of the average). The curves in fig. 1 and the above-mentioned figures make it probable that, during the course of the illness, the chloride content of the fluid is reduced, but they hardly permit of any assumption as to tendencies towards changes in the blood-chloride index during the course of the illness.

Figure 2 shows the state of things as regards the sugar in the fluid and the sugar index during the course of the illness in 10 cases.

The figure shows that the sugar content of the fluid fell in 6 cases, rose in 2, and in 2 cases first fell and then rose. The figure shows, further, that the sugar index fell in 6 cases, rose in 3, and in 1 case first fell and then rose.

As has been stated above, the difference between the average figure for the sugar content of the fluid in the group »8—18 days before death» and in the group »1—7 days before death» is  $6.78 \pm 4.57$  mg per 100 cm<sup>3</sup>, and the corresponding difference for the sugar index  $12.12 \pm 5.34$  (the difference is thus c. 2.3 times larger than the standard error of the average figure). The curves in fig. 2



Sugar-content in fluid in mg.%

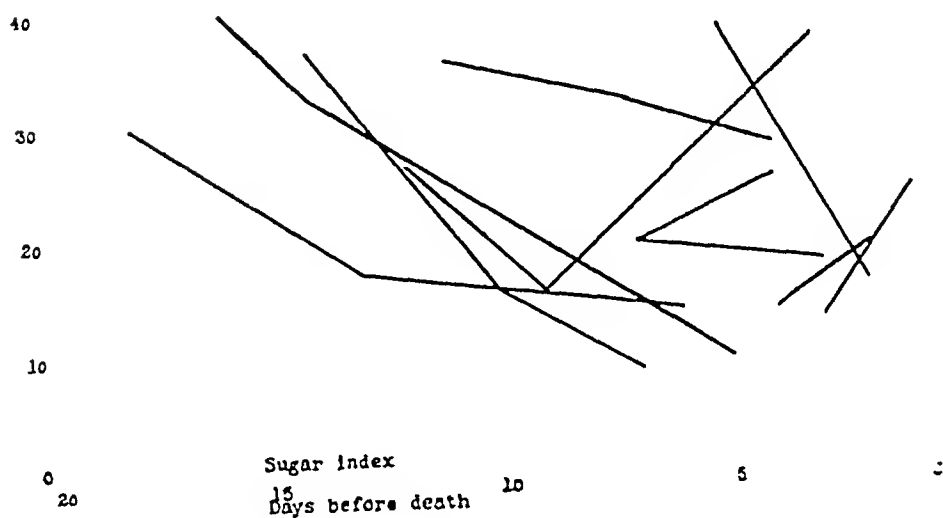


Fig. 2.

and the above figures make it probable that the sugar index in the fluid is reduced during the course of the illness, but they hardly permit of any assumption as to the tendencies towards changes in the sugar content of the fluid during the course of the illness.

The above makes it probable that *during the development of tuberculous meningitis a reduction in the Cl-ion content of the fluid and in the sugar index takes place.*

It is of great interest to know to what extent the determination of the Cl-ion content of the fluid and of the blood-chloride index during the *early stages* of the illness affords any diagnostic information. In an endeavour to throw light upon this question, the difference has been calculated between the average figure for the Cl-ion content of the fluid in the normal material and in the group »8—18 days before death», and also the corresponding difference for the blood-chloride index. This difference is  $13.13 \pm 2.49$  mmol for the Cl-ion content of the fluid, and  $7.55 \pm 2.58$  for the blood-chloride index. The former difference is significant, the latter probably verified. *In the earlier stages of tuberculous meningitis the Cl-ion content of the fluid is thus lower than the normal, and the blood-chloride index probably lower than normal.*

The differences between the normal material and the group »8—18 days before death» are  $30.84 \pm 3.94$  mg per 100 cm<sup>3</sup> for the sugar content of the fluid, and  $32.07 \pm 5.31$  for the sugar index, and both are statistically significant.

In tuberculous meningitis cases the Cl-ion content of the fluid is lower than in any other illness (see below). Apart from the tuberculous meningites, the sugar content of the fluid is also greatly reduced in bacterial meningitis cases. *Thus, from the differential diagnostic point of view, a greatly reduced Cl-ion content of the fluid affords more valuable information than a greatly reduced sugar content of the fluid.*

*Summary of the results.* In tuberculosis meningitis the Cl-ion content of the fluid is  $105.92 \pm 1.52$  mmol (=  $619.63 \pm 8.89$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index is  $132.26 \pm 1.66$ , the sugar content of the fluid is  $30.44 \pm 2.31$  mg per 100 cm<sup>3</sup>, and the sugar index is  $25.12 \pm 2.67$ . All these values are lower than the normal. During the course of the illness a reduction probably takes place in the Cl-ion content of the fluid and in the sugar index. But already during the earlier stages of the illness (8—18 days before

peath) the Cl-ion content, the sugar content of the fluid and the sugar index are lower, and the blood-chloride index probably lower, than the normal. A greatly reduced Cl-ion content of the fluid gives more valuable diagnostic information than a greatly reduced sugar content of the fluid.

### Bacterial meningitis.

As has been mentioned above, all cases of meningitis in which bacteria have been proved in the fluid — except tuberculous meningitis cases — are included in this group.

The material consists of 25 patients, in whom the fluid was examined 56 times.

In table 14 the material has been arranged according to the bacteriological diagnosis of the meningitis. In this table, if we first turn our attention to the column for all the cases, we find that the values are low. The differences between the normal material and the total number of cases of meningitis are  $7.75 \pm 1.16$  mmol, for the Cl-ion content of the fluid,  $10.04 \pm 1.73$  for the blood-chloride index,  $32.23 \pm 3.60$  mg per 100 cm<sup>3</sup> for the sugar content of the fluid, and  $34.72 \pm 3.08$  for the sugar index. All these differences are statistically verified. A low content of Cl-ions in the fluid in bacterial meningitis has been proved earlier by many authors (see table 3), but, as far as I know, no one has proved previously, by a statistical working up of his material, that it differed definitely from a normal material.

From table 14 it appears that the number of cerebrospinal fluids examined in the different groups of bacteria is inconsiderable, and only between the groups *Micrococcus catarrhalis* and Pfeiffer's influenza bacillus can the difference in the average figures be calculated statistically. The average figure for the content of Cl-ions in the fluid and the blood-chloride index is larger in the latter than in the former group, and the differences are  $5.15 \pm 1.79$  mmol and  $1.78 \pm 2.25$  respectively. The former difference is probable, the latter not statistically significant. Thus, *the Cl-ion content of the fluid is probably greater in meningitis caused by Pfeiffer's influenza bacillus than in meningitis caused by Micrococcus catarrhalis.*

The average figure for the sugar content of the c. s. fluid and for



Table  
Bacterial

	Bac-								
	Pneumo- cocci		Meningo- cocci		Strepto- cocci		Micrococcus catarrhalis		
	No.	M	No.	M	No.	M	No.	M $\pm \varepsilon$ (M)	$\sigma$
Cl-ion content of the fluid	8	116.95	7	117.74	2	84.85	13	112.97 $\pm$ 1.13	$\pm$ 4.07
Blood-chloride index ....	8	138.00	7	138.14	1	116.00	13	125.69 $\pm$ 1.00	$\pm$ 3.61
Sugar content of the fluid	6	48.00	7	38.86	.	.	12	30.83 $\pm$ 4.17	$\pm$ 14.43
Sugar index..	6	40.83	7	27.57	.	.	12	25.42 $\pm$ 3.52	$\pm$ 12.18

the sugar is larger in the group *Micrococcus catarrhalis* than in the group Pfeiffer's influenza bacillus, and the differences are  $6.51 \pm 5.38$  mg per 100 cm<sup>3</sup> and  $1.74 \pm 5.34$  respectively. The differences are not statistically significant.

In an attempt to elucidate whether the content of Cl-ions and of sugar in the fluid and the corresponding index show anything as to the prognosis of the illnesses, I have divided the material into two groups, one consisting of material from patients who recovered («healthy patients»), the other comprising material from patients who succumbed («fatal cases»). See tables 15 and 16.

If we first turn our attention to the last main column of each table and compare the values in them, we find that they are higher for the «healthy patients» than in the «fatal cases». The differences are  $5.83 \pm 2.46$  mmol for the Cl-ion content of the fluid,  $6.20 \pm 2.39$  for the blood-chloride index,  $5.65 \pm 6.42$  mg per 100 cm<sup>3</sup> for the sugar content of the fluid, and  $7.59 \pm 5.17$  for the sugar index. The difference for the blood-chloride index is probable from a statistical point of view, and the other differences are not. Thus, in patients suffering from bacterial meningitis the blood-chloride index is probably lower in the patients who succumb than in those who recover. The determination of this index is thus of a certain value for prognosis.

In table 15 it appears that in the «healthy patients» the Cl-ion content of the fluid is about the same during the first 2 weeks of the illness, but rises later. Table 16 shows that in the «fatal cases» the

14.

meningites.

teria

Pfeiffer's influenza bacillus			Staphylococci		Undetermined bacteria		Total		
No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M	No.	M	No.	M $\pm$ $\epsilon$ (M)	$\sigma$
16	118.12 $\pm$ 1.39	$\pm$ 5.57	5	116.38	5	117.80	56	115.34 $\pm$ 1.11	$\pm$ 8.31
15	127.47 $\pm$ 2.01	$\pm$ 7.78	5	137.00	5	136.00	54	131.44 $\pm$ 1.32	$\pm$ 9.69
19	24.32 $\pm$ 3.40	$\pm$ 14.80	5	35.20	4	45.75	53	33.04 $\pm$ 3.06	$\pm$ 22.29
19	23.68 $\pm$ 4.01	$\pm$ 17.48	5	35.20	4	43.00	53	29.08 $\pm$ 2.48	$\pm$ 18.07

Cl-ion content of the fluid falls during the course of the illness. The blood-chloride index falls, while the sugar in the fluid and the sugar index exhibit varying values in both groups. The number of cases in the different groups is small, but the conditions indicated above argue in favour of the view that *the Cl-ion content of the fluid affords more valuable information for prognosis than the blood-chloride index, the sugar content of the fluid or the sugar index.*

In order to show the state of things as regards the Cl-ion content and the blood-chloride index during a very slowly recovering bacterial meningitis, an account of a case is given below.

A 2-year-old boy, who had previously been generally healthy, fell ill 2 days before admission to the Crown Princess Lovisa's Hospital for Children with a bilateral otitis, and paraentesis was done. On the day of admission he suddenly became unconscious, had general convulsions, and on admission to the hospital was in an extremely poor condition. He exhibited pronounced signs of meningitis, and lumbar puncture yielded an extremely turbid fluid, which showed strongly pos. albumin reactions and contained fully 50,000 cells per 3 mm<sup>3</sup>, and an abundance of Pfeiffer's influenza bacilli. He was treated with sulphapyridine for about a month. During the first three weeks his condition was very poor but gradually improved, and after 5—6 weeks he was afebrile, and after about 3 months he had almost entirely recovered.

The patient had lumbar punctures 19 times, the last time

Table 15.  
*Bacterial meningitis which recovered.*

	No. of days after the first symptom									
	0-3		4-6		7-13		14 days-5 months		0 days-5 months	
	No.	M	No.	M	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid . . . .	5	116.44	4	115.98	12	116.14 $\pm$ 1.95	$\pm$ 6.77	13	119.45 $\pm$ 1.73	$\pm$ 6.22
Blood-chloride index . . . . .	5	137.60	3	135.67	12	134.58 $\pm$ 3.57	$\pm$ 12.36	13	130.92 $\pm$ 2.48	$\pm$ 8.94
Sugar content of the fluid . . . . .	4	47.00	4	41.75	12	27.58 $\pm$ 4.19	$\pm$ 14.53	12	38.25 $\pm$ 4.41	$\pm$ 15.26
Sugar index . . . . .	4	41.75	4	30.00	12	24.75 $\pm$ 4.09	$\pm$ 14.17	12	38.08 $\pm$ 5.29	$\pm$ 18.34
									117.43 $\pm$ 1.07	$\pm$ 6.25
									133.70 $\pm$ 1.88	$\pm$ 10.81
									35.78 $\pm$ 3.75	$\pm$ 21.22
									32.53 $\pm$ 3.47	$\pm$ 19.63

Table 16.  
*Bacterial meningitis which succumbed.*

	No. of days after the first symptom								
	0—3		4—6		7—12		0—12		
	$\bar{X}$	M	$\bar{X}$	M	$\bar{X}$	M	$\bar{X}$	$M \pm \epsilon (M)$	$\sigma$
Cl-ion content of the fluid.....	6	115.80	9	112.94	6	105.37	21	$111.60 \pm 2.22$	$\pm 10.17$
Blood-chloride index	5	131.80	9	127.11	6	124.50	20	$127.50 \pm 1.48$	$\pm 6.61$
Sugar content of the fluid.....	6	29.67	5	38.20	5	22.60	16	$30.13 \pm 5.21$	$\pm 20.83$
Sugar index .....	5	21.60	7	31.00	4	18.50	16	$24.94 \pm 3.83$	$\pm 15.33$

c. 5 months after the onset of the illness. After 2 weeks the fluid was sterile (experiments on animals and culture). The findings at the examinations of the fluid appear from the curves in fig. 3.

As is seen in the figure, the number of cells was very high during the first part of the stay in hospital, it then decreased rapidly, but during the first few months remained at several thousand cells per  $3 \text{ mm}^3$ , and after 5 months was still 71 cells per  $3 \text{ mm}^3$ . During the first few weeks 80—90 % of the cells were polynuclear, but the proportion of these gradually decreased, and after a full month there were about as many mononuclear as polynuclear cells, and subsequently the former predominated in number. The sugar index was very low during the first few days (below 10). It then rose gradually, but about 4 months elapsed before it remained definitively at about 50.

The Cl-ion content of the fluid was low during the first three weeks, and its lowest value (105.8 mmol) was met with after 3 weeks' illness. Simultaneously with the patient's definitive improvement the Cl-ion content gradually increased to normal values. On the whole the curve for the blood-chloride index ran parallel with the curve for the Cl-ion content of the fluid. The fact that during the first week, the values for the Cl-ion content of the fluid and for the blood-chloride index were not lower than the lower limit for the normal, is possibly explained by the circumstance

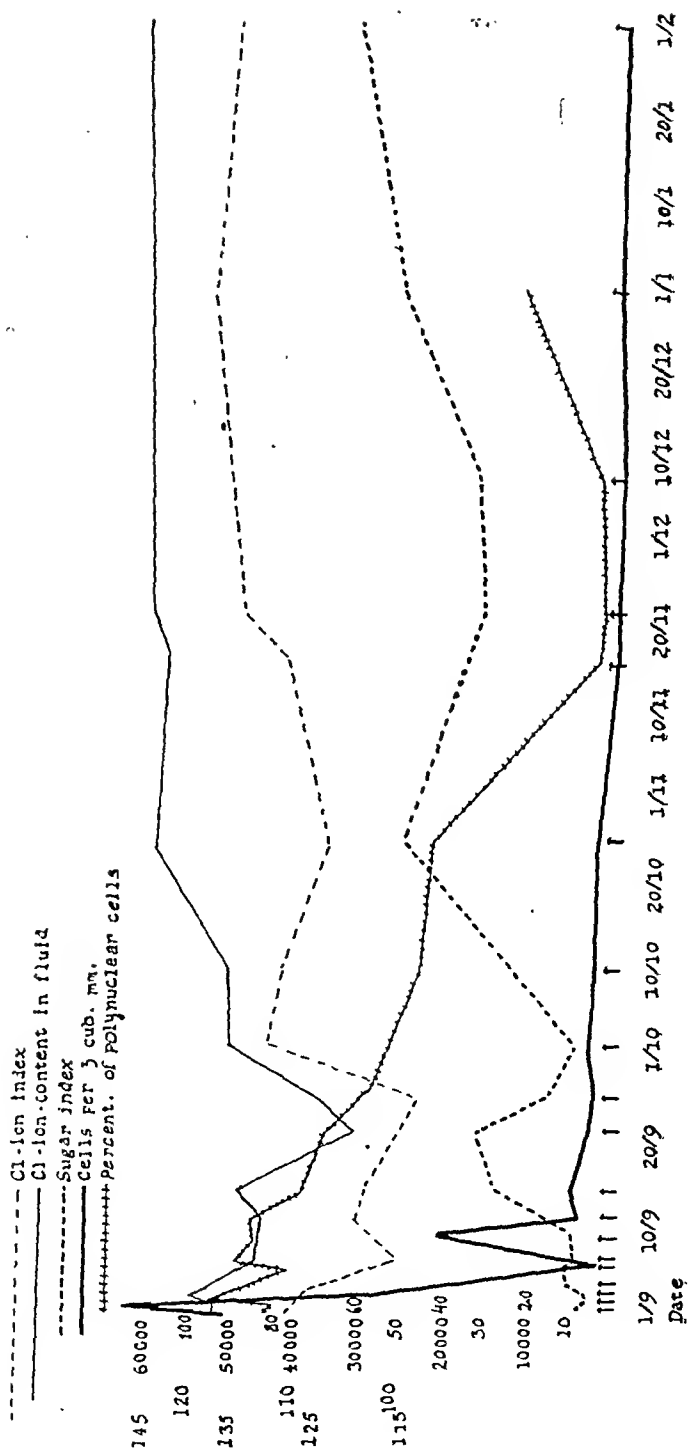


Fig. 3.

that during this period the patient was given subcutaneously an abundance of physiological NaCl.

*Summary of the results.* In bacterial meningitis the Cl-ion content of the fluid is  $115.34 \pm 1.11$  mmol ( $= 674.74 \pm 6.49$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $131.44 \pm 1.32$ , the sugar content of the fluid  $33.04 \pm 3.06$  mg per 100 cm<sup>3</sup>, and the sugar index  $29.08 \pm 2.48$ . All these values are below normal. The Cl-ion content of the fluid is very probably larger in meningitis caused by Pfeiffer's influenza bacillus than in meningitis caused by *Micrococcus catharrhalis*. The blood-chloride index is probably lower in patients who succumb than in those who recover. The Cl-ion content of the fluid possibly affords more valuable information for the prognosis than the blood-chloride index, the sugar content of the fluid and the sugar index.

### Aseptic forms of meningitis.

Under the above heading have been collocated a number of heterogeneous cases, which have the following in common: Clinical signs of a meningeal irritation, increase of cells and albumin in the fluid, sterile fluid, no symptoms of tuberculosis or lues. The delimitation in the direction of encephalitis with meningeal irritation, abortive poliomyelitis and other diseases is naturally difficult, and the limits are often very diffuse. Within the group a differentiation into 3 subgroups has been made.

1. Meningitis lymphocytaria. The patients were acutely ill, with symptoms of meningitis, and all recovered within a fairly short time. The cell increase was moderate (at most, 1,000 cells per 3 mm<sup>3</sup>), and the cells were predominatingly lymphocytes. The group comprises 9 patients (7 children and 2 adults), who together were punctured 25 times.

2. Meningeal irritation in acute infection diseases. This group comprises 20 patients (6 children and 14 adults), who were each only punctured once.

3. Meningitis sympathica. An otitis, sinusitis, osteitis in the vertebrae, or some other inflammatory process was present in the neighbourhood of the meninges, so that a direct connection between the meningeal irritation and the inflammation foci is con-

Table 17.  
*Aseptic meningites.*

	Meningitis lymphocytaria			Meningeal irritation in infection diseases			Meningitis sympathica		Total		
	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M	N	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid . . . .	25	122.54 $\pm$ 0.93	4.67	20	121.05 $\pm$ 0.59	2.64	6	123.32	51	122.05 $\pm$ 0.54	3.85
Blood-chloride index . . . . .	23	141.96 $\pm$ 1.54	7.39	20	141.35 $\pm$ 1.67	7.45	6	143.50	49	141.90 $\pm$ 1.02	7.17
Sugar content of the fluid . . . .	24	56.79 $\pm$ 3.57	17.51	19	70.16 $\pm$ 4.21	18.34	6	69.00	49	63.47 $\pm$ 2.56	17.95
Sugar index . . . .	24	51.46 $\pm$ 2.63	12.87	19	60.21 $\pm$ 2.87	12.53	6	59.83	49	55.88 $\pm$ 1.82	12.73

ceivable, through a general infection need not develop. The group consists of 6 patients (5 children and 1 adult), who were each punctured only once.

It is manifest that, from a theoretical point of view, this grouping to some extent involves uninvestigated conditions. The more detailed mechanism is not clearly established. Further, it is not always easy to decide whether an individual case is to be included in one or the other group.

The result of the investigation appears in table 17.

The difference in the sugar index as between the aseptic meningitis cases and the normal material is statistically verified. (The difference is  $7.92 \pm 2.58$ ). On the other hand no verified difference can be established in the case of the Cl-ion and sugar contents of the fluid. (The differences are  $1.04 \pm 0.64$  mmol and  $1.80 \pm 3.19$  mg per 100 cm<sup>3</sup> respectively). This is also true of the blood-chloride index, which is higher in aseptic meningitis cases than in the normal material (the difference being  $0.42 \pm 1.51$ ).

The number of cases permits of a statistical comparison between »meningitis lymphocytaria» and »meningeal irritation in acute infection diseases». From the table it appears that the average figures for the Cl-ion content of the fluid and for the blood-chloride index are greater in the former than in the latter group. The differences are  $1.49 \pm 1.10$  mmol and  $0.61 \pm 2.27$  respectively. Neither

of them is statistically significant. The average figures for the sugar in the fluid and the sugar index are higher in the last-mentioned group than in the first-mentioned, and the differences are  $13.37 \pm 5.52$  mg per 100 cm<sup>3</sup> and  $8.75 \pm 3.89$  respectively. The former difference is statistically verified, but not the latter.

*Summary of the results.* The Cl-ion content of the fluid in aseptic meningitis is  $122.05 \pm 0.54$  mmol ( $= 713.93 \pm 3.16$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $141.90 \pm 1.02$ , the sugar content of the fluid  $63.47 \pm 2.56$  mg per 100 cm<sup>3</sup>, and the sugar index  $55.88 \pm 1.82$ . The Cl-ion content and the sugar content of the fluid and the blood-chloride index lie within the normal limits, but the sugar index is below normal. For the Cl-ion and sugar contents of the fluid and for the blood-chloride and sugar indexes there is no definite difference between Meningitis lymphocytaria and meningeal irritation in acute infection diseases.

Meningeal irritation without increases in albumin or cells  
in the c. s. fluid.

This group consists of patients who were suffering from some infection disease, and who exhibited clinical symptoms of a meningeal irritation, but without albumin and cell increases in the fluid. This group is thus near the sub-group of aseptic meningitis cases which have been termed »meningeal irritation in acute infection diseases», and the delimitation as against the normal material is somewhat diffuse, although in it are included only patients with slighter infections.

The material consists of 11 patients, who were each punctured once. The average figure for the Cl-ion content of the fluid was 120.03 mmol ( $= 702.18$  mg per 100 cm<sup>3</sup>), for the blood-chloride index 142.50, for the sugar content of the fluid 72.77 mg per 100 cm<sup>3</sup>, and for the sugar index 65.15.

In this group may be included patients suffering from tuberculosis, in whom vomiting and an inconsiderable stiffness of the neck aroused suspicions of the meningitis. Lumbar puncture yielded a perfectly physiological fluid, however, and the further course showed that the patients were not suffering from the meningitis. The group comprised 7 patients, who were punctured 11 times altogether.



Table 18.  
*Poliomyelitis (all the cases).*

	Paretic form			Abortive form			Total cases		
	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid .....	56	124.45 $\pm$ 0.36	$\pm$ 2.72	28	123.11 $\pm$ 0.49	$\pm$ 2.60	84	124.00 $\pm$ 0.30	2.75
Blood-chloride index	54	144.83 $\pm$ 1.02	$\pm$ 7.51	27	143.26 $\pm$ 1.24	$\pm$ 6.43	81	144.31 $\pm$ 0.80	7.21
Sugar content of the fluid .....	55	61.11 $\pm$ 1.34	$\pm$ 9.96	27	61.96 $\pm$ 1.85	$\pm$ 9.63	82	61.39 $\pm$ 1.09	9.87
Sugar index .....	54	58.44 $\pm$ 1.78	$\pm$ 13.06	27	61.78 $\pm$ 2.42	$\pm$ 12.58	81	59.56 $\pm$ 1.44	13.00

The average figure for the Cl-ion content of the fluid was 120.31 mmol, for the blood-chloride index 140.50, for the sugar content of the fluid 66.09 mg per 100 cm<sup>3</sup>, and for the sugar index 56.82.

The inconsiderable number of cases in these two groups does not permit of any mathematical calculation of whether it differed from the normal material. The values probably lie within the limits for the normal material, however.

### Poliomyelitis ac.

The diagnosis of the paretic form of poliomyelitis usually presents no difficulties, while the diagnosis of the abortive form may often be difficult. All the patients in the present material fell ill with symptoms typical of poliomyelitis during a period when the disease was prevalent in Stockholm. They suffered from headaches and stiff necks. The fluid showed pos. albumin reactions and contained at least 30 cells per 3 mm<sup>3</sup>.

The material comprises 77 patients, 37 of whom were under and 40 over 15 years of age. 56 of the patients had the paretic and 21 the abortive form of the disease. The number of cerebrospinal fluids examined was 84.

Table 18 shows the results of the examination of the paretic and the abortive forms, and of all the cases.

If we compare the whole poliomyelitis material with the normal material, we find that the figures for the Cl-ion content of the fluid and the blood-chloride index are higher in the former, while the

Table 19.  
*Paretic poliomyelitis.*

	No. of days after the first symptom.													
	0—2			3—5			6—8			9—14			0—14	
	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	$\sigma$	No.	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid . . . .	15	123.61 $\pm$ 0.68	$\pm$ 2.63	9	123.94	20	125.54 $\pm$ 0.59	$\pm$ 2.64	12	124.07 $\pm$ 0.80	$\pm$ 2.76	56	124.45 $\pm$ 0.36	$\pm$ 2.72
Blood-chloride index . . . . .	15	146.13 $\pm$ 2.34	$\pm$ 9.06	8	147.25	19	142.11 $\pm$ 1.45	$\pm$ 6.31	12	145.92 $\pm$ 1.83	$\pm$ 6.35	54	144.83 $\pm$ 1.02	$\pm$ 7.51
Sugar content of the fluid . . . .	15	65.00 $\pm$ 2.73	$\pm$ 10.58	9	60.56	20	60.05 $\pm$ 2.32	$\pm$ 10.38	11	58.18 $\pm$ 3.07	$\pm$ 10.19	55	61.11 $\pm$ 1.34	$\pm$ 9.96
Sugar index . . . .	15	60.40 $\pm$ 3.37	$\pm$ 13.06	9	62.78	20	56.00 $\pm$ 3.20	$\pm$ 14.29	10	56.50		54	58.44 $\pm$ 1.78	$\pm$ 13.06

**Table 20.**  
*Abortive poliomyelitis.*

	No. of days after the first symptom									
	0—2		3—5		6—8		9—93		0—93	
	$\frac{\Sigma}{S}$	Average	$\frac{\Sigma}{S}$	Average	$\frac{\Sigma}{S}$	Average	$\frac{\Sigma}{S}$	Average	$\frac{\Sigma}{S}$	$M \pm \epsilon (M)$ $\sigma$
Cl-ion content of the fluid .....	6	124.00	6	123.32	7	121.57	9	123.58	28	$123.11 \pm 0.49$ $\pm 2.60$
Blood-chloride index ..	6	139.67	6	147.67	7	143.14	8	142.75	27	$143.26 \pm 1.24$ $\pm 6.43$
Sugar content of the fluid .....	6	58.83	6	62.67	7	67.14	8	59.25	27	$61.96 \pm 1.85$ $\pm 9.63$
Sugar index .....	6	62.00	6	69.33	7	60.71	8	56.88	27	$61.78 \pm 2.42$ $\pm 12.58$

figures for the sugar content of the fluid and the sugar index are higher in the latter material. The difference is  $0.91 \pm 0.46$  mmol for the Cl-ion content of the fluid,  $2.83 \pm 1.38$  for the blood-chloride index,  $3.88 \pm 2.19$  mg per 100 cm<sup>3</sup> for the sugar content of the fluid, and  $4.24 \pm 2.33$  for the sugar index. None of these differences are statistically verified, and the investigation affords no support for an assumption that, in the respects mentioned, poliomyelitis patients differ from healthy persons.

From table 18 it appears that the paretic form shows a higher Cl-ion content of the fluid and a higher blood-chloride index, but a lower sugar content of the fluid and a lower sugar index than the abortive form of the disease. The differences mentioned are  $1.34 \pm 0.61$  mmol,  $1.57 \pm 1.61$  and  $0.85 \pm 2.28$  mg per 100 cm<sup>3</sup> and  $3.34 \pm 3.00$  respectively. None of these differences are statistically significant, and the investigation gave no support for an assumption that, in the respects mentioned, the paretic and abortive forms of the disease differ from each other.

The tables 19 and 20 show that the Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes vary fairly little, and that there is no definite tendency towards an increase or decrease in them during the course of the illness.

*Summary of the results.* In poliomyelitis ac. the Cl-ion content of the fluid is  $124.00 \pm 0.30$  mmol ( $= 725.40 \pm 1.76$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $144.31 \pm 0.80$ , the sugar content of the fluid  $61.39 \pm 1.09$  mg per 100 cm<sup>3</sup>, and the sugar index  $59.56 \pm 1.44$ . All these figures lie within the normal limits, and in neither

Table 21.

*Epilepsy.*

	Cases without convulsions during the last 24 hours			Cases with convulsions during the last 24 hours		Total cases		
	N	M $\pm$ $\epsilon$ (M)	$\sigma$	N	M	N	M $\pm$ $\epsilon$ (M)	$\sigma$
Cl-ion content of the fluid ....	54	123.80 $\pm$ 0.34	2.49	9	119.89	63	123.24 $\pm$ 0.37	2.97
Blood-chloride index .....	52	140.96 $\pm$ 1.01	7.25	8	138.25	60	140.60 $\pm$ 0.93	7.22
Sugar content of the fluid ....	21	61.00 $\pm$ 3.09	14.17	5	73.40	26	63.38 $\pm$ 2.73	13.91
Sugar index ..	20	63.90 $\pm$ 3.31	14.81	5	63.20	25	63.76 $\pm$ 2.78	13.88

the parietic nor the abortive form do they show any definite tendency to rise or fall during the course of the disease. There is no evidence that the Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes vary in the parietic and abortive forms of the disease.

*Epilepsy.*

When the illness first makes its appearance it may often be difficult to diagnose epilepsy. Nearly all the patients in this material, however, had had the disease for many years, and doubtful cases are not included.

The material comprises 62 patients (27 children and 35 adults). One of the patients was punctured twice, the others once, and the number of cerebrospinal fluids examined was thus 63. See table 21.

A comparison with the normal material shows that in cases of epilepsy, the figures for the Cl-ion content of the c. s. fluid are higher, while those for the sugar content of the fluid, and the blood-chloride, and sugar indexes are lower than in normal cases. The differences are  $0.15 \pm 0.51$  mmol,  $1.89 \pm 3.31$  mg per 100 cm<sup>3</sup>,  $0.88 \pm 1.46$  and  $0.04 \pm 3.32$  respectively. None of the differences are statistically significant. If the normal material is compared with epilepsy cases which have not had convulsions during the last 24 hours, the same conditions are found. According to statements pub-

lished earlier, the Cl-ion content of the fluid is normal, but the material on which this statement is based is small, and the figures are not worked up statistically. The largest are HAMILTON's (1925), FREMONT-SMITH and DAILEY's (1925) and LICKINT's (1928) materials, which comprise 16, 11 and 10 cases respectively.

It appears from table 21 that the average figures for the Cl-ion content of the fluid, and the blood and sugar indexes are higher in the group »cases without convulsions during the last 24 hours» than in the group »cases with convulsions during the last 24 hours»; but the average figure for the sugar content of the fluid is higher in the latter than in the former group. The differences are  $3.91 \pm 0.76$  mmol,  $2.71 \pm 2.36$ ,  $0.70 \pm 5.72$  and  $12.40 \pm 5.53$  mg per 100 cm<sup>3</sup> respectively. Only the difference for the Cl-ion content of the fluid is statistically verified.

In the literature I have only found one mention of epileptics who were punctured in connection with convulsions, namely HAMILTON's. His 2 patients had a Cl-ion content of the fluid which did not differ from those of the other epileptics.

The number of »cases with convulsions during the last 24 hours» is somewhat small, as appears from table 21. To obtain a larger material of children whose fluids had been examined during the same 24 hours that they had had convulsions, I have collocated in table 22 the above-mentioned material of epilepsy convulsions with a material consisting of 6 children with initial convulsions.

Table 22.  
All the cases of convulsions.

	Initial convulsions during the last 24 hours		Epileptic convulsions during the last 24 hours		All the cases with convulsions during the last 24 hours		
	No.	M	No.	M	No.	$M \pm \varepsilon (M)$	$\sigma$
Cl-ion content of the fluid . . . .	6	118.43	9	119.89	15	$119.31 \pm 0.92$	3.56
Blood-chloride index . . . . .	6	134.33	8	138.25	14	$136.57 \pm 2.03$	7.59
Sugar content of the fluid . . .	6	74.17	5	73.40	11	$73.82 \pm 5.07$	16.83
Sugar index . . . . .	6	65.33	5	63.20	11	$64.36 \pm 3.57$	11.86

None of these 6 children had any increase of albumin or cells in the fluid, and the children rapidly recovered from the pharyngitis which gave rise to the convulsions.

If a comparison is made between the group «all the cases with convulsions during the last 24 hours» and the normal material, it is found that the figures for the Cl-ion content of the c. s. fluid and for the blood-chloride index are lower, while those for the sugar content of the fluid and the sugar index are higher, in the former than in the latter group. The differences are  $3.78 \pm 0.98$  mmol.,  $4.91 \pm 2.32$ ,  $8.55 \pm 5.41$  mg per 100 cm<sup>3</sup> and  $0.56 \pm 4.01$ . Only the first difference is statistically significant.

As has been shown above, for the epilepsy patients the values for the Cl-ion content of the fluid lie within the normal limits. There is no reason to suppose that pharyngitis patients in general have a low Cl-ion content of the fluid (several patients with pharyngitis are included in the normal material). Thus, the conclusion is reached *that children who have had convulsions during the last 24 hours before lumbar puncture have a low Cl-ion content of the fluid.*

*Summary of the results.* In epilepsy the Cl-ion content of the fluid is  $123.24 \pm 0.37$  mmol, ( $720.95 \pm 2.16$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $140.60 \pm 0.93$ , the sugar content of the fluid  $63.38 \pm 2.73$  mg per 100 cm<sup>3</sup> and the sugar index  $63.76 \pm 2.78$ . All these values are in good agreement with the normal values. Epilepsy patients who have had convulsions during the last 24 hours before the puncture have a lower Cl-ion content of the fluid than other epilepsy patients.

Table 23.

*Tumours in the central nervous system.*

	Cerebral tumours						Spinal marrow tumours Cistern fluid
	Ventricle fluid			Lumbar fluid			
	$\frac{N}{O}$	$M \pm \varepsilon (M)$	$\sigma$	$\frac{N}{O}$	M	$\frac{N}{O}$	M
Cl-ion content of the fluid	17	$124.34 \pm 0.92$	3.81	7	122.71	4	125.28
Blood-chloride index.....	16	$150.44 \pm 2.38$	9.51	6	138.67	4	140.75

## Tumours in the central nervous system.

The majority of the tumours were gliomas and meningiomas, but several other kinds of tumours are represented. In all the cases the diagnosis was verified at operation or autopsy.

The material consists of 28 patients, and the cerebrospinal fluid was examined once only in each case. The results of the investigation appear in table 23.

As there is no normal material of ventricle fluid, it cannot be established whether the values in the table for the Cl-ion content of the fluid and for the sugar index are normal or not. In CHRISTIANSEN's (1936) material, comprising 13 cerebral tumours, the NaCl content of the ventricle fluid varied between 681 and 747, and averaged 734 mg NaCl per 100 cm<sup>3</sup>. This NaCl content agrees fairly well with my own. The material of lumbar-punctured cases with cerebral tumours, and of cistern-punctured spinal marrow tumours, is too small to justify any definite conclusions, but there can hardly be a question of any considerable divergencies from the normal.

*Summary of the results.* In cases of cerebral tumours the ventricle fluid contains  $124.34 \pm 0.92$  mmol Cl ( $= 727.39 \pm 5.38$  mg NaCl per 100 cm<sup>3</sup>) and the blood-chloride index is  $150.44 \pm 2.38$ .

Table 24.

*Various nervous diseases.*

	Cl-ion content of the fluid.		Blood- chloride index		Sugar content of the fluid		Sugar index	
	N <sup>o</sup>	M	N <sup>o</sup>	M	N <sup>o</sup>	M	N <sup>o</sup>	M
Hydrocephalus .....	3	131.90	2	140.00	2	61.50	2	51.00
Cerebral hemorrhage .....	1	126.9	1	130.4	—	—	—	—
Thrombosis cerebri .....	1	125.5	1	152.2	—	—	—	—
Pachymeningitis haemorrhagica int.	1	122.6	1	138.4	1	51	1	62.3
Cephalalgia .....	2	121.60	2	144.50	2	76.50	2	84.50
Sclerosis dissiminata .....	7	124.39	7	137.14	3	64.33	3	70.33
Polyneuritis .....	3	125.20	3	146.00	3	66.67	3	60.67
Little's disease .....	13	123.83	13	138.62	13	63.46	13	66.38
Idiotia and Imbecillitas .....	3	125.90	3	136.33	3	50.00	2	64.00

Table 25.

Percentage of examinations, which fall outside the normal limits, calculated at  $2\sigma$ ,  $2.5\sigma$  and  $3\sigma$ .

	Cl-ion content of the fluid				Blood-chloride index				Sugar content of the fluid				Sugar index			
	No.	Outside			No.	Outside			No.	Outside			No.	Outside		
		$2\sigma$	$2.5\sigma$	$3\sigma$		$2\sigma$	$2.5\sigma$	$3\sigma$		$2\sigma$	$2.5\sigma$	$3\sigma$		$2\sigma$	$2.5\sigma$	$3\sigma$
Normal material .....	33	3.0	0	0	33	6.1	0	0	30	6.6	0	0	30	3.3	3.3	0
The-meningitis 8—18 days before death ..	15	80.0	80.0	80.0	15	33.3	11.1	6.7	14	85.7	78.6	64.3	14	92.9	85.7	71.4
" 1—7 " ..	20	100.0	100.0	100.0	20	25.0	25.0	15.0	20	85.0	80.0	80.0	18	100.0	100.0	88.9
" Total cases .....	35	91.4	91.4	91.4	35	28.6	20.0	11.4	34	85.3	79.4	73.5	34	93.3	90.9	78.8
Bacterial meningitis. Recovered .....	34	55.9	50.5	44.1	33	30.3	21.2	15.2	32	65.6	59.4	56.3	32	68.8	59.4	53.1
" Succumbed .....	21	80.9	80.9	76.2	20	65.0	40.0	15.0	16	75.0	75.0	75.0	16	81.3	81.3	75.0
" Total cases .....	55	65.5	61.8	56.4	53	43.4	28.2	15.4	48	68.8	64.6	62.5	48	72.9	66.6	60.4
Aseptic meningitis. Lymphocytaria .....	25	20.0	16.0	4.0	23	0	0	0	24	16.6	12.5	12.5	24	12.5	4.2	4.2
" In acute infection dis-																
" ases .....	20	35.0	30.0	15.0	20	10.0	5.0	5.0	19	26.3	10.5	5.3	19	36.8	15.7	5.3
" Total cases of aseptic																
" meningitis .....	51	25.5	19.6	7.8	49	4.1	4.1	4.1	49	18.4	10.2	8.2	49	20.4	8.2	4.1
Poliomyelitis. Paretic form .....	56	21.4	5.4	3.6	54	9.3	5.6	1.9	55	0	0	0	54	11.1	3.7	1.9
" Abortive form .....	28	17.9	7.1	3.6	27	14.8	7.4	0	27	0	0	0	27	7.4	3.7	3.7
" Total cases .....	84	20.2	5.9	3.6	81	11.1	4.2	1.2	82	0	0	0	81	9.9	3.7	2.5
Epilepsy .....	63	12.7	7.9	7.9	60	11.7	8.3	6.7	56	19.2	11.5	11.5	56	12.0	8.0	0
Convulsion diseases .....	15	33.3	26.7	20.0	14	14.3	7.1	0	14	9.1	9.1	9.1	14	0	0	0



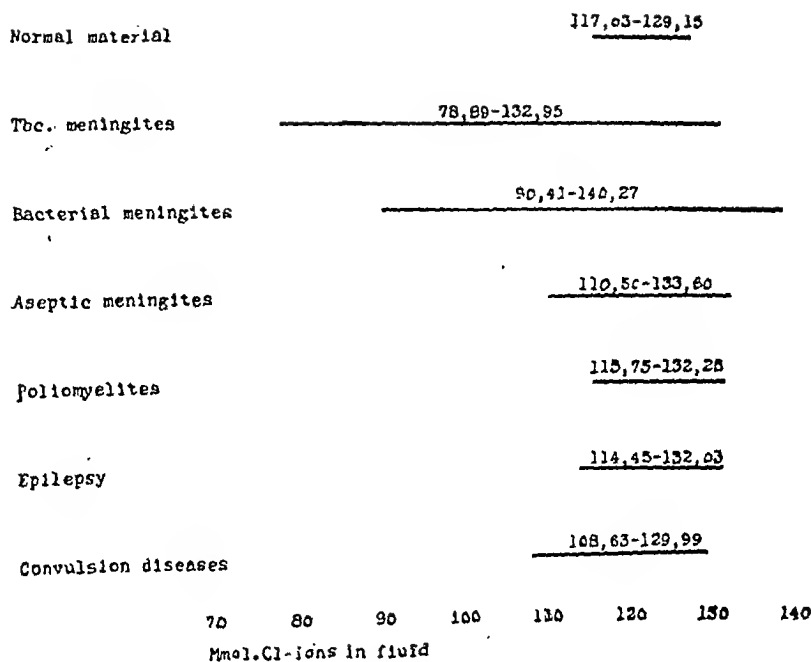


Fig. 4.

Other diseases in the central and peripheral nervous system.

In table 24 a number of nervous diseases have been collocated. The number of cases in each group is too small to justify any general conclusions. With the exception of patients with hydrocephalus, in whom the Cl-ion content of the fluid is probably high, the values for the other diagnoses lie within the normal limits.

What proportion of the cerebrospinal fluids examined in cases of various morbid conditions fall outside the normal limits?

The average figures are calculated above for the Cl-ion content and the sugar content of the fluid, and for the blood-chloride and sugar indexes. Further, it has been calculated to what extent the averages which are based on investigations of different morbid conditions differ from the average figures in a normal material. In table 25 is indicated what percentage of the number of exami-

nations fall outside the normal limits when the dispersion has been calculated at  $2\sigma$ ,  $2.5\sigma$ , and  $3\sigma$ .

It appears from the table that, in tuberculous and bacterial meningitis cases, the majority, and in some other diseases (convulsion diseases, aseptic meningitis) a number of cerebrospinal fluids have a Cl-ion content which lies outside the normal. Further, it appears clearly that in all the disease groups the number of examinations which gave the Cl-ion content as outside the normal is larger than those which gave a blood-chloride content outside the normal. *The Cl-ion content of the fluid is thus of greater diagnostic value than the blood-chloride index. If the Cl-ion content of the fluid is compared in the same manner with the sugar content of the fluid and the sugar index, it is found that these examinations are of about the same diagnostic value and that they supplement each other well.*

## A survey of the diagnostic value of the Cl-ion content of the fluid.

*A survey of the diagnostic value of the Cl-ion content of the fluid.*

Fig. 4 shows the field within which the Cl-ion content of the fluid in different diseases varies, when the limits for the normal variation range are calculated at  $3\sigma$ . The figure shows to what extent the range of variation reaches below or above the normal range. In table 25 are only given the numbers outside the normal range of variation without regard to the sign (if positive or negative).

As will be seen, the normal material has the smallest and tuberculous meningitis the largest variation range. For the majority of the disease groups the variation range extends farther below the lower limit for the normal than above the upper limit for the normal. The variation range for tuberculous and bacterial meningitis extends far down, and *if the Cl-ion content of the fluid is lower than 108 mmol (= 631.8 mg NaCl per 100 cm<sup>3</sup>) the patient has a tuberculous or bacterial meningitis.* The variation range for tuberculous meningitis extends farthest down, and *a Cl-ion content of the fluid below 90 mmol (= 526.5 mg NaCl per 100 cm<sup>3</sup>) is pathognomonic for the disease.*

## SUMMARY.

A survey of the literature shows that many authors have occupied themselves with determinations of the Cl-ion content of the cerebrospinal fluid. A number of these authors have also determined the relation between the Cl-ion content of the fluid and of the blood. Light has been thrown on many relevant problems by these earlier investigations. The majority of the authors mentioned have, however, not determined the margins of error of the methods employed, nor had at their disposal a large investigation material, nor worked up their results statistically.

The purpose of the present work is to try to determine the diagnostic value, firstly, of the Cl-ion content of the fluid, and secondly, of the relation between the Cl-ion content of the fluid and of the blood, and whether these investigations afford more of diagnostic value than determinations of the sugar content of the c. s. fluid and of the sugar index.

*The material* comprises 428 cerebrospinal fluids from 355 patients, of whom 189 were between 6 months and 15 years old, and the other 166 patients were more than 15 years old.

*The method* employed for the Cl-ion determinations in the fluid and the blood was electrometric microtitration. Its sources of error were found to be c. 0.5% and 2 % respectively. For determinations of the sugar content of the fluid and the blood Hagedorn-Jensen's method was employed.

To illustrate the *importance of vomiting* for the Cl-ion content of the fluid, and for the relation between the Cl-ion content of the fluid and of the blood (this relation multiplied by 100 is designated the blood-chloride index) the author used a poliomyelitis material. This was divided into three groups, namely, 1. patients who had vomited during the last 24 hours before the punctures, 2. patients

who had not vomited during the last 24 hours before the punctures, 3. patients about whom it was not known whether they had vomited or not during the last 24 hours before the punctures. It proved that in this material the vomiting had not had any significance in the respects mentioned. The question must be left open as to whether the vomiting plays any rôle for patients whose vomiting was more pronounced than in the case of the poliomyelitis patients.

The author has tried to answer the question whether there is any difference in the Cl-ion content of the lumbar and cistern fluids, firstly, by comparing the Cl-ion content of the lumbar and cistern fluids in patients who were lumbar- and cistern-punctured at the same time, and secondly, by examining different portions of the fluid obtained with fractional lumbar punctures, and finally, by comparing the Cl-ion content of the fluid in patients who were lumbar-punctured with the Cl-ion content of the fluid in patients who were cistern-punctured. No difference as between the Cl-ion content the lumbar and cistern fluids could be proved.

The author has tried to establish *whether the Cl-ion content of the fluid and the blood-chloride index bears any relation to the patient's age*, by determining the correlation between the age and the Cl-ion content of the fluid, and between the age and the blood-chloride index in the poliomyelitis material. No age correlation could be established.

*The Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes in the normal conditions.* As lumbar and cistern punctures cannot be considered entirely risk-free, the author has not attempted to obtain a material consisting of fluids from completely healthy persons. As a substitute for such a material the author selected from his clinical cases certain cases in which there was reason to assume that the contents of Cl-ions and sugar in the fluid and the blood were the same as those in healthy persons. This so-called normal material comprises 33 patients. In these very slightly affected patients, who were not suffering from diseases of the central nervous system, and in whose fluids no morbid changes were established, the Cl-ion content of the fluid was  $123.09 \pm 0.35$  mmol ( $= 720.1 \pm 2.05$  mg NaCl per 100 cm<sup>3</sup>), the blood-chloride index  $141.48 \pm 1.12$ , the sugar content of the fluid  $65.27 \pm 1.90$  mg

per 100 cm<sup>3</sup> and the sugar index  $63.80 \pm 1.83$ . The range of variation for the Cl-ion content of the fluid extends from 118.7 mmol (=694.4 mg NaCl pr 100 cm<sup>3</sup>) to 126.8 mmol (=741.8 mg NaCl pr 100 cm<sup>3</sup>), for the blood-chloride index from 128 to 156, for the sugar content of the fluid from 48 to 89 mg pr 100 cm<sup>3</sup> and for the sugar index from 50 to 81.

*The Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes in morbid conditions.*

*Tuberculous meningitis.* The material comprises 35 lumbar fluids from 16 patients. Both the Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes are lower than normal. Even in the earlier stages of the illness the Cl-ion and sugar contents of the fluid and the sugar index are lower, and the blood-chloride index probably lower than normal. A greatly reduced Cl-ion content of the fluid affords more valuable information for the diagnosis the-meningitis than a greatly reduced sugar content in the fluid.

*Bacterial meningitis.* In this group are included all the cases of meningitis in which bacteria were proved in the fluid, except the tuberculous meningitis cases. The material consists of 56 cerebrospinal fluids from 25 patients. Both the Cl-ion content and the sugar content of the fluid and the blood-chloride and sugar indexes are lower than normal. The Cl-ion content of the fluid is probably higher in meningitis caused by Pfeiffer's influenza bacillus than in meningitis caused by Micrococcus catarrhalis. The blood-chloride index is probably lower in the patients who succumb than in those who recover. The Cl-ion content of the fluid possibly affords more valuable information for the prognosis than the blood-chloride index, the sugar content of the fluid, or the sugar index.

*Aseptic meningitis.* In this group have been collocated a number of heterogeneous cases which have the following in common: Clinical signs of meningeal irritation, increase in cells and albumin in the fluid, sterile fluid, no symptoms of tuberculosis or lues. The material comprises 51 cerebrospinal fluids from 35 patients. Within the group a division into 3 sub-groups has been made. These are meningitis lymphocytaria, meningeal irritation in acute infection diseases, and meningitis sympatica. Both the Cl-ion and sugar contents of the fluid and the blood-chloride index are within the normal limits, but the sugar index is lower than normal.

*Meningeal irritation without increases in cells or albumin in the fluid.* The material consists of 22 cerebrospinal fluids from 11 patients suffering from some acute infection disease, and 7 from patients suffering from tuberculosis. The values for the Cl-ion and the sugar contents of the fluid, and for the blood-chloride and sugar indexes probably lie within the normal limits.

*Poliomyelitis ac.* The material comprises 84 cerebrospinal fluids examined from 56 patients suffering from the paretic and 21 patients suffering from the abortive form of the disease. Both the values for the Cl-ion and the sugar contents of the fluid, and the blood-chloride and sugar indexes lie within the normal limits. These values do not show any difference as between the paretic and the abortive forms of the disease, and in neither of the two forms of the disease have they any definite tendency to rise or fall during the course of the disease.

*Epilepsy.* The material comprises 63 cerebrospinal fluids from 62 patients. Both the Cl-ion and the sugar contents of the fluid, and the blood-chloride and sugar indexes lie within the normal limits. Epilepsy patients who have had convulsions within the last 24 hours before the puncture have a lower Cl-ion content of the fluid than other epilepsy patients.

*Tumours in the central nervous system.* The material comprises 28 cerebrospinal fluids from 28 patients; 17 patients suffering from cerebral tumours were ventricle punctured. The ventricle fluid in the latter had a Cl-ion content of  $124.34 \pm 0.92$  mmol ( $= 727.39 \pm 5.38$  mg NaCl per 100 cm<sup>3</sup>), and the blood-chloride index was  $150.44 \pm 2.38$ . As there is no normal material of ventricle fluids, it cannot be determined whether these values lie within the normal limits.

For a number of *other diseases in the central nervous system* the Cl-ion and sugar contents of the fluid and the blood-chloride and sugar indexes were determined. The number of cases in each disease group is too small to justify any general conclusions, but there will probably be no considerable divergencies from the normal.

A *tabular survey* of what proportion of the cerebrospinal fluids examined fall outside the normal limits in different morbid conditions shows that the Cl-ion content of the fluid is of greater diagnostic value than the blood-chloride index. The table shows,

further, that the Cl-ion content of the fluid is of about the same diagnostic value as the sugar content of the fluid and as the sugar index, and that these investigations supplement each other.

*Extremely low values of the Cl-ion content of the fluid.* If the Cl-ion content of the fluid is lower than 108 mmol (= 631.8 mg NaCl per 100 cm<sup>3</sup>), the patient has either a tuberculous or a bacterial meningitis. A Cl-ion content of the fluid lower than 90 mmol (= 526.5 mg NaCl per 100 cm<sup>3</sup>) is pathognomonic for tuberculous meningitis.

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*THE MASTICATORY EFFECT*





# THE MASTICATORY EFFECT

A NEW TEST AND AN ANALYSIS OF MASTICATION IN  
MORE OR LESS DEFECTIVE SET OF TEETH

BY

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LUND

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## Preface.

This work is divided into two sections. In Part I a new mastication test is discussed, which is based on older tests that have, however, been very much modified. Further, a method has been worked out of calculating the effect of mastication, which has resulted in a mastication coefficient. The aim has been to make the method possible for practical use, and also to render it sufficiently easy to use for mass investigations.

In Part II an investigation has been made of the chewing in persons of different sex and age (children, adults and old people), and in groups with sets of teeth of varying nature. In the first place, the quality of the teeth has been investigated in the above-mentioned groups, made from an average population. The number of chews and the effect of mastication have been analysed, and, finally, an investigation has been made of chewing with full dentures.

When working out the methods, the author was given working facilities in the Physiological Institution, Uppsala. I should like to offer my warm thanks to Professor TORSTEN TEORELL for the kindness and interest he has shown me, and the advice I have had from him. This applies in particular to the working out of colorimetrical determinations of the test portions' degree of reduction.

In the statistical treatment of the material, place at the State Institute of Race Biology was put at my disposal. I would like to thank the Head of the Institute, Professor GUNNAR DAHLBERG, for his kindness here, and for the advice he gave me during the statistical analysis. I should further like to thank Miss INGEGERD PLYHR, Miss MARTHA ADLER and Mr GUSTAF KUJAHN for their painstaking work of calculation.

The translation has been carried out by CAROLYN HANNAY, M. A., and to her, too, I offer my warm thanks.

*Bertil Dahlberg.*



## Chapter 1.

### Survey of the literature.

If we leave out of account the importance of the teeth for appearance and speech, it is plain that their sole task is to divide up the food into small pieces. In odontology attention has primarily been paid to diseases connected with the teeth and the parodontium. As a matter of fact, no very great interest has been shown to the function of the teeth under physiological and pathological conditions, although the effect of mastication no doubt could be called a central problem within odontology.

It is, however, not only of theoretical but also of practical importance to get an idea of the masticatory powers in different sets of teeth. When, for example, a conscript is to be judged for military service, it stands to reason that some regard must also be paid to the state of his teeth and his powers of mastication. It has, however, not been possible to reach generally accepted norms by applying viewpoints of military hygiene to the teeth, since there has been no very exact knowledge as to how far the powers of mastication decline when the condition of the teeth gets worse. One of the few authors who has made any statement on this point is KANTOROWICZ, 1932, who says that the experiences during the World War 1914—1918 would show that 3—3½ pairs of molars or bicuspidals should ensure fitness for military service. No investigations seem to have been made to substantiate rules of this kind.

In practical dentistry, a closer knowledge of the masticatory effect and its relation to the number of teeth is necessary — for example, when deciding whether a patient requires prosthesis. There is no doubt that an almost complete loss of teeth definitely indicates artificial ones. There is a stage between extremely defective sets of teeth and almost complete ones where, according to Kantorowicz, it can be said that »wo man die Grenze für die Notwendigkeit des Ersatzes ziehen will bleibt in gewissem Masse der Willkür überlassen». It is, of course, a perfectly tenable view

that every defect in the set of teeth should be restored as far as possible, not only to keep the masticatory powers at as high a level as possible, but above all to prevent secondary consequences on the antagonist teeth and adjacent teeth, and also on the set as a whole. It is difficult in practical work to act consistently according to such norms, and it is therefore of particular interest, when deciding if the patient requires artificial teeth, to have a clear idea of the masticatory powers in relation to the number of teeth.

Kantorowicz maintains that the powers of mastication are palpably diminished with the loss of five or more units, so that prosthesis is needed. In this connection, one pair of molars in an antagonist position is regarded as one unit, and other pairs of teeth as half a unit. This rule is not, however, based on investigations showing that just such a loss of teeth is definitely detrimental to masticatory powers to this extent. At present it is not possible to motivate fixed indications for prosthetic replacement, since it is not known how many teeth of different types can be missing without serious detriment to the powers of mastication. In other words, it is not possible to give the patient definite reasons for the degree of toothlessness at which replacements are necessary. The result of this is that it is often the patient himself who decides when such treatment is to be undertaken, and this almost always means that the treatment is begun unnecessarily late; i. e. not until the patient himself cannot stand the situation any longer and, in many cases, only after pronounced anomalies in the set of teeth and their position have further impaired the powers of mastication.

Finally, it may be recalled in passing that a connection may exist between impaired masticatory powers and disturbances in the gastro-intestinal canal. These problems have met with lively scientific interest and a large number of investigations have been carried out to show this connection in more detail. It is fairly well agreed that, if the gastro-intestinal canal is pathologically disturbed, poor mastication has a harmful effect on the course and duration of the complaint. Actually, though, we have no exact knowledge as to the importance of the teeth in this respect. Questions of this kind can only be answered when we are able to decide both how far an incomplete set of teeth decreases the masticatory powers, and the extent to which the gastro-intestinal canal receives far too inadequately chewed food when teeth are missing.

Although the problems connected with the powers and the effect of mastication have both theoretical and practical interest, the odontological literature contains only a few works which deal with them in more detail. The present survey will deal first with the methods used for determining the effect of mastication, and then give a short account of the results obtained by them.

*The methods used.*

The first to deal with the problem was CHRISTIANSEN, 1922. The aim of his investigation was to determine whether complete prostheses, mounted according to the articulation method, were better able to reduce food than such as were mounted according to the occlusion method — i. e. in an ordinary hinge-articulator. Christiansen's procedure in his experiments was first to supply several suitable subjects with a double set of complete prostheses, the teeth being in articulation in the one and in occlusion in the other. When the patients had got used to both of these, they were given a certain substance to chew, which was then examined. The substance chosen as test material was cylinders of Spanish hazel-nut for the first experiments; later, however, cocoanut was used, though Christiansen says that this latter is tougher and more troublesome to chew, and gives results inferior to those obtained with hazel-nuts. He gives no reasons why he continues to use cocoanut. It is further to be noted that neither the weight nor the volume of the portions are given.

The experiments were carried out in the following way. The patient was made to chew the test material 50 times, and then spit it out into a measuring-glass with a volume of 500 c. cm. The glass was filled with water up to the 500 line and the contents poured into a strainer, after which the same amount of water was poured through five times. The apparatus consisted of four containers one above the other, each with a straining-net with meshes of  $\frac{1}{3}$ ,  $\frac{1}{2}$ , 1 and 2 mm. a side. After straining, the four fractions were dried in a drying- cupboard at 100° C, and when constant weight had been reached — which was calculated to take place after an hour — each fraction was weighed. Each quantity was then reckoned in per cent of the total weight.

As Christiansen has given no data as to the reliability of the method, it is not known how far the results vary from one occasion to the next, when the experiments are repeated on the same



person. It is therefore impossible to determine how far the method yields satisfactory results. There is, however, reason to suppose that a straining in the simple apparatus and with the small amount of rinsing-water that Christiansen used would give fairly uncertain figures.

Christiansen is nevertheless the first to present and seek to solve the problem by testing out the effect of mastication on a definite material. The method he gives has been taken up by later authors. Thus, in an investigation in 1928 using on the whole the same methods, BALTERS tried to compare the effect of mastication with prostheses made with and without regard to the individual path of the condyles. The alterations made by Balters in the method were that the size of the straining-nets was increased (0.30, 0.75, 2 and 3 mm.), and that the strainers were rinsed with water from a rubber tube attached to the water-tap. This rinsing method is an improvement; a source of error is, however, to be found in there having been no arrangements made to standardize the rinsing. Balters gave neither the time for rinsing, the water pressure nor the amount of water used during straining. In this investigation, too, the test material was cocoanut. The fractions were dried in a drying cupboard at 100°, and weighed.

In 1932 JUUL investigated the masticatory powers in children with normal and abnormal occlusion. The method is the same as that used by Christiansen and Balters, cocoanut being used as test material to a weight of 6.5 g. per portion. The holes in the strainers had about the same size as in the one used by Balters. It should, however, be mentioned that the meshes of the finished nets, which are mass-produced are not all the same size, since the wires cross each other without being fixed at each intersection. Differences between the meshes can clearly be seen in figures given in the paper. Juul gives the mean size of the meshes and uses a network where they are on an average 0.4, 1, 1.5 and 2 mm.

An investigation of the masticatory powers of adults with their own teeth was carried out by ASCHER in 1938. The method differs only in a few points from that of Christiansen. Instead of cocoanut, Ascher used peeled Brazil-nut for test material. The quantity per portion, 3.5 g., was about half the amount of cocoanut Juul tried on children. Comparing cocoanut und Brazil-nut from the point of view of mastication, there is reason to suppose that the latter is more suitable as test material, since it has a

fairly homogeneous consistency; cocoanut, on the other hand, has a tendency to disintegrate during mastication along lines of cleavage implicit in its structure. When determining the coarseness of the network in the strainers, Ascher has used the rules in *Deutsches Arzneibuch* for strainers used in sorting chopped herbal drugs and pulverized medicaments. He decided on meshes of 0.30, 0.75, 2 and 3 mm. a side. In the sorting, drying and weighing of the fractions, Ascher's method tallies with those of previous investigators.

The masticatory powers in adults with their own teeth have also been investigated by GELMAN, 1932. The method he used is relatively simple and differs in important points from that of Christiansen. The test material consisted of sweet almonds, with about four almonds, corresponding to approximately 5 g. of substance, to each portion. The test subjects were made to chew not a fixed number of times but for a fixed period, on an average 50 seconds; the author has not shown why this latter method should be preferred to the former one. The number of chews per time unit varies very considerably, since different people chew at different rates according to habit or temperament.

In contrast to Christiansen, Gelman dried the fractions over a water bath instead of in a drying-cupboard at 100°, before the sorting out of the particles into different sizes. He considers drying in a drying-cupboard inadvisable, as he is afraid the chewed particles might change their shape during the process. It goes without saying, that there is shrinking of the particles, since the test material contains water which drying causes more or less to evaporate. If the particles are first sorted by means of the strainers, there is nothing to prevent the drying being carried out afterwards, provided it is taken far enough to be expected to give constant weight. The objection can, however, be made to drying the chewed fractions in a drying cupboard, that there is no guarantee the process will, as regards different-sized particles, be the same from case to case. Obviously the largest particles will not, in the same time, lose as much water as the smallest ones. Gelman's method of first drying the chewed mass over a water bath and then sorting the dried particles is uncertain, as such a drying will probably be fairly uneven and subject to chance. If, on the one hand, the drying goes on too long, the particles shrink and the straining is affected. On the other hand, if the mass is only slightly dried, it affects the

results of the weighing. It is plain that Gelman did not consider these points of view, since he states he dried the mass for 10—40 minutes, and thus did not use a constant time.

The straining was done by shaking the dried mass through a single strainer with round holes 2.4 mm. in diameter. The method of investigation is very rough; only the part of the chewed material remaining in the strainer has been preserved. The weight of the weighed fraction which remains in the strainer was then calculated in per cent of the undried mass, i. e. 5 g.

From a practical viewpoint it may be objected that the test materials used in the investigations described must have been difficult to chew for persons with poor teeth. After all it is first and foremost the masticatory powers of such persons that there is special reason for testing. It is further of importance that the test material should be standardized, homogeneous and indissoluble in saliva. It is probably doubtful whether hazel-nut, cocoanut, Brazil nut and almond are, in the respects mentioned above, what is required in a test material. It is likely that the material, at all events to some extent, changes its character when kept due to possible drying.

For the straining, most investigators have used a network of four sizes, two of which had meshes so small that only very tiny particles could get through. When investigating the effect of mastication efforts should be made as far as possible to base the investigation on the fact that it is the power of the jaws and the teeth to decimate ordinary food which is of interest. Consequently, the above choice of test material and of strainers has not been appropriate. Too fine strainers have been used.

The method of sorting out the chewed portions into different fractions has not been standardized. The drying of the fractions gives no sure guarantee that the different-sized particles are dried to the same extent from case to case. The separate fractions remaining after the drying do not weigh much, and the values obtained after weighing are not made more reliable by the fact that this is done with precision scales to the fourth decimal place, as the straining method is probably very uncertain.

Summing up, it should thus be possible to say that, up to now, not very suitable test materials have been used, and that the methods which have been worked out have been unsatisfactory and must have given very unsure values. These judgments are based on a general discussion of the methods. No investigator

has made an analysis of the standard error of measurement, and there are therefore no exact data as to their reliability. This being so, it is desirable both to work out, if possible, a more reliable method, and also to investigate the limits of error for the method which may finally be achieved.

A short account will now be given of the results obtained by the above-mentioned authors in their investigations with the methods described into the masticatory powers of a number of persons.

### *The results obtained.*

As has already been said, CHRISTIANSEN, 1922, tried to investigate whether complete prostheses, mounted according to the articulation method, function better in mastication than those mounted according to the occlusion method. His material consists of 7 persons with complete prosthesis of each kind. The author submits figures of the distribution into different fractions in articulation prosthesis and occlusion prosthesis, and draws the conclusion that the articulation prosthesis functions better. Actually, there are no criteria for judging whether the difference in his material is a true one or has arisen at random. Seeing that, as has been said before, the method must be fairly uncertain, and as he investigated only 7 persons, it is very possible, and even probable, that the moderate differences he found are purely chance ones. It is therefore impossible to venture a definite statement on the basis of the published material. Christiansen has also investigated the masticatory powers in 10 persons with complete prostheses, mounted in such a way that the teeth of the one side were set in articulation and those of the other side in occlusion. The aim with this was that the patient should chew exclusively with the articulation side on the one occasion, and with the occlusion side on the second. The results from this experimental series show, on the whole, smaller fractions on the coarsest strainer and higher fractions on the finer strainers in chewing with the articulation side. In a number of cases the difference is not marked; this the author considers due to the fact that the teeth on the occlusion side happened to be set comparatively correctly. The author has also compared the effect of mastication in several patients with defective sets of teeth with and without artificial replacement, and, further;

4 patients with complete sets and 4 where they were defective. No statistical analysis of the figures obtained by the chewing tests has been made. The author only publishes the figures and lets them speak for themselves.

An investigation, also concerning a comparison between complete prostheses of different construction, was made by BALTERS in 1928. First, 4 toothless patients with complete sets of artificial teeth were investigated for the effect of mastication. In so doing the author got extremely varying values, and came on this account to the conclusion that even a comparison between the masticatory powers in the same patient provided with two different prostheses is not possible with the methods used.

The author decided to compare the masticatory affect of complete prostheses mounted both with and without regard to the individual path of the condyles. Two patients were equipped with prostheses where the teeth in the articulator had been set up and ground in with consideration paid to the path of the condyles of the patient. After allowing the patient time to get used to the set, the masticatory effect was investigated. The same prosthesis was put into the articulator again and the teeth ground in with the path of the condyles in horizontal position and with the same height for the bite. After this the masticatory effect was again tested.

By arranging the experiments in this way, the same conditions were obtained with the two chewing tests except for the factor which the author wished to test. He found no difference in the masticatory effect »outside the normal range of variation», but at the same time he stresses the fact that the results do not prove it unnecessary to take into account the slope of the condyles when making complete prostheses.

Compared with Christiansen, Balters is remarkably chary with his conclusions and has his eyes open to the uncertainties which attend the method of testing.

In a later work BALTERS, 1930, has investigated the masticatory powers in a patient who was made to chew successively with four complete prostheses mounted with the same height of the bite, the same base and the same front teeth, but with grinding teeth of different construction and material. Here the author considered he found marked differences in masticatory powers between the different prostheses. However, it is hardly possible to reach any definite conclusion on the basis of the figures Bal-

ters submitted, since no computation has been made of the standard error of the testing.

How effectively a complete prosthesis functions depends on several factors, as e. g., the height and firmness of the crista, the way the jaws are placed in relation to one another, the articulation of the teeth, and so on. A number of experiences have been empirically collected as to how a prosthesis is to be constructed to function satisfactorily. It is, however, the patient's own experiences which ultimately decide whether the prosthesis is to be considered »satisfactory». Now, when judging his prosthesis, the patient has as a rule only slight criteria to go on, and seldom has the chance to compare different models. Even if the information he gives has a certain value, it would be of advantage to get in addition an objective gauge of the effectivity of the prosthesis by means of a test of the masticatory effect. We could then, as Balters tried, also go a step further and make prostheses identical save in the one or other respect, and thus, by a systematic investigation, find out the relation different constructions bear to one another as far as function is concerned.

The effect of anomalies in the set of teeth on the masticatory powers has not been studied in much detail. It has been assumed without any definite grounds that practically every clear anomaly means a decline of these powers. JURL, 1932, has taken up this problem for investigation and collected a material consisting of 27 children with normal occlusion and 26 with abnormal occlusion. The children, who all had complete sets of teeth, were from 11—17 years of age.

The author compares the effect of mastication, expressed in per cent of the 4 different fractions, in children with normal and abnormal occlusion, and finds that the latter have larger fractions on the coarsest strainer. For the three finer strainers, the situation is reversed. The results show that the masticatory powers in children with anomalous sets of teeth are on an average worse than in those with normal sets of teeth. It is, however, difficult to estimate the results obtained, since no more detailed information is given as to the degree of dental anomalies. Further, the author has not calculated the standard error of the tests, so that no closer analysis of the figures is possible.

A work of ASCHER, 1938, deals with a material of adults, some with complete and some with defective sets of teeth. The author presents 68 tables with figures of chewing tests, but the tables

do not show how far the tests were carried out by the same person; nor is the number of investigated subjects given.

The investigation material is divided according to the number of teeth into three groups. Under the first group come the complete sets, and, as well, such as have an unbroken row of teeth only on the one side. Characteristic for this group is the fact that the fraction on the coarsest strainer, is very small and as a rule equals nought. The sum of the fractions in the two finer strainers is larger than those in the two coarser ones. Under the second group come the slightly defective sets of teeth with up to 6 mastication units missing (one mastication unit means according to Aseher, one molar pair in articulation position, and a half unit a pre-molar pair or incisor pair in articulation position). The difference between this group and the first one is small, and it is also characterized by the sum of the finer fractions being greater than that of the coarser. The third group with more than 6 mastication units missing shows no »correlation» between the masticatory effect and the number of mastication units. With 30 chews, the coarser fractions preponderate, and it is only after 80 chews that there is a levelling out to the advantage of the finer fractions. The author comes to the conclusion that a loss of more than 6 mastication units indicates prosthetic replacement.

It is, however, impossible to judge how far the conclusions which the author considers himself able to draw are motivated by the numerical result submitted. It has not been statistically treated, and the figures vary not inconsiderably. A statistical treatment is impossible, on account of missing data as to how far the tests have been made by the same or different persons; nor is it known to what extent the author may possibly have wanted to demonstrate results by submitting selected examples. The figures given naturally point in the direction given by the author, without our being able to consider his conclusions to be proved.

GELMAN, 1932, has carried out about 250 masticatory function tests, of which a small number are described in his work. As has already been said, the author had his test subjects chew for a certain period. One table shows that, of 7 persons, two needed to chew for 30 seconds and the rest for 50 seconds for practically no remains of the chewed material to remain in the only strainer he used. The 'optimal' chewing period was set at 50 seconds, and this time was chosen as a unit for the chewing tests.

The author investigated 38 persons, for whom he gives figures for masticatory effect and the number of articulating pairs of teeth. According to the tables, it appears that 4 investigated persons with, on an average, 12.5 articulating pairs of teeth have a mean figure of 96.4 per cent for the part of the test material passing the strainer. It further appears that 17 persons with, on an average, 9.8 articulating pairs had a corresponding figure of 68.7 per cent, and the mean for 13 persons with an average of 7 articulating pairs was 54.1 per cent. It is finally seen that 4 persons with an average of 3.2 articulating pairs of teeth had a mean of 17.9 per cent.

The author finds that a loss of 6—9 articulating pairs of teeth — i. e. on an average, 7 pairs — decrease the masticatory powers by half, which state he considers to give a fairly unsatisfactory masticatory effect.

There is no possibility of determining how far the differences found by the author have arisen at random, since he submits no figures for the individual cases and has not made calculations about the standard error. For the rest, he sets up a strange formula for the effectivity of the chewing, which includes not only the period of mastication and the amount of material chewed, but also a factor characterized as the psychosomatic condition of the test subject and 'die Lebensverhältnisse'.

It may be advanced, by way of *summary*, that investigations hitherto carried out indicate that it should be possible by chewing tests to measure the masticatory effect in persons with sets of teeth of different character. Meanwhile the methods hitherto used must be regarded as very unsure, but it should be possible to improve them. The investigations which have been carried out as to how different people chew, comprise comparatively small and selected materials, which have not been submitted to any statistical analysis. For this reason, no clear picture of the masticatory effect under different conditions has as yet been obtained. In summarizing the literature Sognnaes 1941 says that the studies on masticatory efficiency »have not been extensive enough, nor have they been sufficiently well controlled to allow any definite conclusions».



The first part of this investigation concerns method. An attempt is made to work out a method suitable for determining the masticatory effect. Different materials have been tried out to ascertain their suitability as test materials. An apparatus for straining has been constructed, and special methods of computing the effect of mastication by reducing the test material have been worked out. The author has arrived at a standardized method which should be tolerably exact, and at the same time can be used for mass investigations.

In the second part this method is used for testing the masticatory effect in children, grown-up persons, old people and persons with full prostheses, of both sexes. This material has been statistically analysed, firstly in regard to the extent of the defects in the teeth and the number of contacts between the teeth. Secondly, the chewing has been investigated and the number of chews in persons differing as to age, sex and the character of their sets of teeth, has been statistically analysed. The third and main point of the investigation is the masticatory effect in varying conditions of the teeth and in groups of different age and sex. In particular the variability and factors which cause the variability are investigated. Finally the masticatory effect in persons with full prostheses is compared with the effect of mastication in persons with teeth of their own.

In the statistical analysis only elementary methods have been employed. The reader is referred to any textbook, for instance: Gunnar Dahlberg: *Statistical Methods for Medical and Biological Students* (1940).

## Part I.

# Methods of a mastication test

## Chapter 2.

### Theoretical discussion of the requirements in a mastication test.

As appears from the survey of the literature, there is at present no satisfactory method of gauging the function of the teeth in mastication. A procedure is required which is standardized and analysed as to its reliability. Not until a satisfactory test has been arrived at will it be possible to investigate the masticatory powers in a complete and in a more or less defective set of teeth, and get something to go on when judging both the need and the effect of a prosthesis. Only when it can be determined how far an incomplete number of teeth means a decrease in the masticatory powers and thus not so good reduction of the food, can further investigation be made into the importance of a deficient set of teeth for digestion, the general state of health, and the like.

A test method for investigating the masticatory powers calls first and foremost for a suitable material to chew. It is, further, necessary to work out a method to establish how effectively the chewing is completed. We shall begin by discussing the question of a suitable material, and then go on to determining the degree of its mastication.

#### *Materials for a mastication test.*

At a primitive stage of culture, when the main food substances are either raw or very little prepared, the teeth play a very much more important part in mastication than is the case in civilized conditions. Our usual food is chosen and prepared in such a way that the demands we have on the powers of our teeth are really very small.

The food substances included in a normal diet can be roughly divided up according to their consistency into the following groups:

1) *soft*:

e. g. butter, cheese, eggs, minced meat, fish, soft bread, boiled potatoes, boiled root-crops, stewed fruit;

2) *firm — tough*:

e. g. beef, pork, liver, kidneys;

3) *firm — brittle*:

e. g. hard bread (rye-vita), biscuits, rusks;

4) *firm*:

e. g. raw vegetables, raw root-crops, raw fruit.

For persons with few teeth or complete prostheses, some of these substances are difficult or impossible to chew. Most difficulty is probably encountered in tough boiled beef. Persons with poor teeth often cut the meat into small pieces and swallow it down without chewing at all. On the other hand, the chewing of raw fruit and hard bread, for example, would seem, according to reports from the patients, to offer less difficulties, provided that the mouthfuls are not too big.

As regards the nature of normal food, a tabulation has been made, based on reports communicated by Kungl. Socialstyrelsen (Royal Social Board) of the consumption of foodstuffs in normal Swedish households for the fourth quarter of the year 1940. It is found that firm and tough food substances (meat etc. of different kinds) constitute about 4.5 per cent, firm substances about 5 per cent and firm and brittle substances 2 per cent. The main part of the substances normally consumed belong to the group of soft foods, namely 88.5 per cent.

When choosing material for a mastication test, the following theoretical viewpoints should in the first place be observed.

I. The material for chewing should be of a character to resemble ordinary food to some extent. It should not be so easy to chew that persons with practically no teeth can press it into bits with their tongue and alveolar processes, but it must not either be so difficult to chew as to disable persons with extremely bad sets of teeth from making the test. The material should be chosen within these limits.

II. The material for chewing should not swell, or dissolve in water or saliva.

III. During chewing, the material should be reduced in such a way that it is possible to establish the degree of reduction. When being crushed, it must not be divided along preformed directions of cleavage, as is the case with hard bread; nor must it stick together, as with chewing-gum.

From a practical point of view, it is necessary that the material is standardizable, will keep for more than a very short period and has a pleasant or at any rate an indifferent taste.

As has been said already, boiled beef is unduly difficult to chew for persons with insufficient teeth, and does not in other respects agree with the demands set. Liver, kidneys or such are conceivable materials for chewing, though hardly suitable — for one thing because they have a somewhat varying character and are thus difficult to standardize.

The hard-boiled white of a hen's egg answers most of the demands which have been set, though, however hard it is boiled, it is of so soft a consistency that it can be chewed even by toothless people.

Of the vegetable food substances, raw carrot may be considered just difficult enough to chew. Carrot does not break up along preformed directions of cleavage; it is, however, somewhat soluble and also swells in water. The edges of the chewed particles are not sharp, so that a sorting into different sizes will be uncertain. There is a difference in consistency between the fresh and the stored carrot, and this means that one cannot have access to a constant material if the investigation is to spread over some time.

Examples of non-food substances, which are possible as test material, are synthetic rubber, indiarubber and gelatin, hardened by formalin.

Synthetic rubber of the kind used by draughtsmen differs from usual sorts of rubber by virtue of its porous nature. The material fulfils the theoretical demands which have been drawn up, but it has an unpleasant taste and gives, when chewed, a choking sense of dryness.<sup>1</sup>

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<sup>1</sup> Only a small quantity has been obtainable for testing purposes.

For comparison with synthetic rubber, indiarubber of soft, porous character can also be tested. This can be reduced to small pieces by people with good sets of teeth, though not completely so, since the chewed particles have a tendency to cohere. Further, indiarubber can be chewed by persons with bad sets of teeth only with the greatest difficulty or not at all.

One would rather expect gelatin hardened by formalin to be best able to answer the demands for a suitable material for mastication. The food substances to which this material can, with regard to its consistency, most be likened are liver boiled hard or boiled veal gristle. (This latter is not, of course, reckoned as a foodstuff but is, alas, not infrequently included as an ingredient in cooked veal.) Gelatin can vary as regards gelatinous content, and it is therefore possible to test different consistencies. By hardening it in formalin, the mass is changed, so that it no longer dissolves in water. There is no very precise knowledge as to the effect of the formaldehyde on gelatin at hardening. The water is combined to the gelatin micelle. A number of water molecules are absorbed on the surface of the micelle and others are enclosed between the micelles. It has been assumed that the effect of the formaldehyde in hardening would strengthen the 'cross communications' in the network of polypeptide chains forming gelatin micelles, which means that the gelatin cannot be dissolved in water or the water molecules penetrate between the micelles.

#### *Subdivision of the test portion.*

In empirical testing of the material, as in making the chewing test, the degree to which the chewed portion has been reduced must be determined. The most feasible procedure would seem to be to follow earlier investigators and divide up the chewed mass into a suitable number of fractions, where each fraction can be thought to contain particles of about the same size. A further concern is to determine the quantity of particles within each fraction. How suitably to perform the fractionation depends on the character of the test material. When the chewed mass does not contain water, as is the case with synthetic rubber or indiarubber, for example, the fractions may be dry-sifted and weighed. If, on the other hand, the material is one containing water, e. g. carrot or gelatin hardened by formalin, mastication gives particles which cannot be sorted by means of dry-sifting,

for fear of drying up and because of their tendency to stick together. Under such circumstances, the straining must be done in water.

In the investigation presented here, the latter method has been used. When determining the number of strainers and the size of the holes, it is advisable to choose these according to the size of the particles present in a test portion; this latter should be divided up into enough fractions for each one of them to be comparatively small. Not until this has been done can it be justifiably assumed that the particles in one fraction are of an order of magnitude lying between the holes in the two strainers limiting the fraction. It is advisable to take too many rather than too few strainers, so that relatively small and numerous fractions are obtained. It is always possible in the statistical treatment to put the fractions together, if necessary, but they cannot on the other hand be divided up further, if found too few. Previous investigators have been content with a few fractions (at most four), and a finer division of the portion for chewing is surely desirable.

Running water must be used in straining to prevent larger particles from getting lodged in the holes and hindering the passage of smaller ones. The running water should have a rotating component, so that the particles are moved about over the holes, and at the same time a downward component, so that they are sucked through. An irregularly shaped particle with different sizes in different planes will in this way have repeated possibilities for getting through.

To get comparable results from straining, the method must be standardized as regards the amount of water passing through the apparatus per time unit. Standardization implies that the time of straining and the water pressure must both be constant.

Different ways can be taken of determining the *size of the fractions*. Thus, it is possible to get an idea of the particles' distribution in the test portion by weighing the different fractions separately; any water must, of course, first be removed. If the test material contains water, there is a risk that the actual particles, too, will dry up. There is obviously difficulty in standardizing the drying process so that water is removed to the same extent in different fractions. The method has the further disadvantage that drying and weighing waste time. This procedure therefore seems very little suited to a mass investigation.

Instead of weighing the different fractions, it is, however, possible to count the number of particles which remained in the less fine and coarse strainers. Such a count does not take much time and should give a reliable result. The difficulties do not begin until the counting of the particles in the finer strainers. On this account, the finer fractions can suitably be determined by measuring the volume after sedimentation of the particles in graduated glass tubes. (This method has actually been used.) This method has the advantage of weighing in that the size of the different fractions is determined without the particles being exposed to air-drying. The method is quick, and should be suitable for use in mass investigations.

All the same, both methods have the drawback that the results consist of a series of figures for the sizes of the different fractions. The figures show that, if fractions with small particles are large and fractions with large particles are small, the reduction is more complete than if the opposite is the case. Nevertheless, it is difficult to form from the figure series obtained a clear idea of the degree of the test portion's reduction. The figures are difficult to survey as a whole, and a simple expression for the degree of reduction is desired.

Now the act of chewing means that the portion is reduced so as to give a larger total surface than in its original state. The enlargement of the surface per volume unit has the advantage that the digestive juices have better play. It is in this way that the chewing of food is of importance for the digestion. In principle, it should therefore be reasonable to try and get a simple gauge of the effectivity of mastication by calculating the total surface of the fractions and relating them to the volume of the test portion. In this way a *mastication coefficient* is obtained which gives a simple expression for the degree of reduction, and which has a close connection to the physiological problem in question. An assumption now readily presenting itself is that the particles are on an average regular polyhedrons. On the basis of different assumptions it is possible, when the number of the particles in the fractions is known, to calculate the total volume and test if it agrees with the known volume of the test portion. It is further possible to calculate the total surface and then get the mastication coefficient — i. e. the surface area per volume unit.

It can now be assumed that the particles in the fractions on an average correspond to cubes, mixed with shapes of larger

volume more or less spherical, and also with shapes of less volume corresponding to octahedrons or the like. In reality, of course, the question is, throughout, one of particles with very irregular shape. It can further be assumed that the particles correspond on an average to octahedrons, and we can seek to prove this.

Let us, therefore, assume that the particles are, on an average, in the form of cubes and that the measurement of their side diagonal lies between the diameter of the holes in strainers that have been passed through and those that have not. If this mean diameter is called  $d$ , the side of the cube is obtained in the expression  $\frac{d}{\sqrt{2}}$ . From the side of the cube we get its volume

from the expression  $\frac{d^3}{2\sqrt{2}}$ , and the volume of the fraction from

the expression  $N \frac{d^3}{2\sqrt{2}}$ , where  $N$  is the number of particles in

the fraction. We further assume that the particles have on the average, the shape of octahedrons, and can then in analogous

wise calculate their volume from the formula  $2 \frac{B \cdot h}{3}$ , where  $B$  is

the basal surface of the pyramid and  $h$  is the height. The diagonal of the octahedron's base is the same as the side diagonal of the cube, so that the side of the octahedron is obtained from the

expression  $\frac{d}{\sqrt{2}}$ , the basal surface being  $\frac{d^2}{2}$  and the height in the

one pyramid  $\frac{d}{2}$ ; the octahedron's volume will be  $\frac{d^3}{6}$ . The volume

of the last fractions can be calculated after it has been determined by sedimentation of the particles in graduated glass tubes. It is then necessary, however, to change these volumes into number of particles, which can be done by determining the number of particles per volume unit. The volume of the fraction is then

calculated from the formula  $vn \frac{d^3}{6}$ , where  $v$  = the volume obtained

through sedimentation and  $n$  = the number of particles per sedimented volume unit. (For cubes of course the corresponding

formula is  $vn \frac{d^3}{2\sqrt{2}}$ .)



The surface of the test portion can now also be calculated in the same way. If we assume that the particles are cubical, we get the surface of the fraction by multiplying the number of particles by  $3 d^2$  (the side of the cube is  $\frac{d}{\sqrt{2}}$ , as before). The surface of an octahedron with the same base diagonal as the side diagonal of the cube is got from the formula  $d^2\sqrt{3}$ , if we proceed from the same assumptions as in the determination of the volumes. For fractions with volumes determined by sedimentation, the formula  $vn d^2\sqrt{3}$  is used, where the signs mean the same as above. For cubes the formula is  $vn3d^2$ .

The following pages will give an account of the investigations made with regard to different chewing material and different methods of dividing up the test portions by straining into different fractions etc. to the end of achieving a standard method for mass investigations. Here the author will only anticipate by saying that the method finally preferred is one based on a division of the test portion by means of straining into 10 fractions. In fractions 4—10 the number of particles are counted, and in fractions 1—3 (the finest ones) the mass of particles is determined by sedimentation in graduated glass tubes. A determination of particles per c. cm. is further made in the sedimented fractions. Finally, the surface and volume of the test portion are determined under the assumption that the particles in fractions 4—10 corresponded on an average to cubes, and those in fractions 1—3 to octahedrons. The mastication coefficient — i. e. surface area per c. cm. — is reckoned out from the calculated surface and volume. In Chapter 6, the tenability of these assumptions will be tested in more detail on the basis of empirical investigations. These data have been given in advance, as the reader needs them to be able to follow the account of what is now coming.

## Chapter 3.

### Investigation of different test materials.

In the foregoing chapters different materials have been discussed with regard to their suitability in mastication tests. Even if gelatin hardened by formalin would seem in theory to be most suitable, it is necessary for more definite conclusions to test this empirically.

A small number of people have been made to chew fixed portions, one after the other, of all the test materials discussed above. The test subjects consisted of conscripts, half of which had 'extremely good' sets of teeth, and half 'bad'.<sup>2</sup> At the tests, each person on one and the same occasion chewed in turn pieces of gelatin hardened by formalin, hard-boiled white of hen's egg, raw carrot, synthetic rubber and indiarubber. There was one series of portions chewed until they felt ready to be swallowed, and two series where the portions were chewed 40 times. The results of tests with different materials have been compared with regard to the difficulty in reducing the material to small pieces, and also with regard to errors of measurement in re-straining the test portion.

Average values for the size of the fractions in the different materials are given in Table 1.

Comparing the mean sizes of the fractions after 40 chews from test subjects with good and poor sets of teeth, we find that the degree of reduction in good sets is greater than in poor ones. The fractions in good sets are, compared with the others, greater for the strainers 1—4 and smaller for strainers 6—10. The differences in reduction between good and poor sets of teeth are most outstanding in the fractions with the largest and the smallest particles. As it is difficult to get a general survey of the average

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<sup>2</sup> With regard to the limits of good and bad sets of teeth respectively, cf. Chap. 11.

TABLE 1.

Distribution of tests on different fractions (means). For the fractions 1—3 the volume is given in c. cm., for the fractions 4—10 in number of particles. The number of the fraction indicates the diameter of the holes in the strainer in mm.

Fraction	Gelatin 10 %	Gelatin 15 %	Gelatin 20 %	Carrot	White of egg	Synthetic rubber	India- rubber
Extremely good set of teeth: mastication at discretion.							
1	1.6	2.2	2.5	1.8	2.2	3.3	0.18
2	3.2	4.1	4.5	2.8	2.6	3.7	0.37
3	4.0	4.4	4.6	3.3	2.9	3.3	0.55
4	53.2	60.0	59.8	35.6	33.8	32.5	11.1
5	27.6	26.7	25.2	22.8	19.5	16.5	11.1
6	11.4	11.3	10.4	10.7	10.0	7.8	10.2
7	5.0	5.9	4.5	4.9	5.8	4.2	9.2
8	2.2	2.2	2.2	2.6	3.7	1.9	6.3
9	0.78	0.78	0.73	0.54	2.0	0.79	4.4
10	0.46	0.46	0.78	0.63	2.8	0.94	7.2
	$n = 41$	$n = 41$	$n = 41$	$n = 41$	$n = 41$	$n = 33$	$n = 11$
Bad set of teeth: mastication at discretion.							
1	0.44	0.63	0.82	0.77	1.5	1.6	0.08
2	1.0	1.4	1.6	1.4	1.8	1.9	0.14
3	1.8	2.1	2.4	1.7	2.0	2.1	0.18
4	34.0	36.5	42.2	21.2	25.9	34.3	4.7
5	24.7	26.8	29.2	17.2	16.9	20.4	4.1
6	15.9	16.7	18.0	12.7	9.9	12.5	4.2
7	10.8	9.9	11.1	8.7	7.0	8.2	4.0
8	6.0	5.8	5.9	5.5	4.7	4.2	4.3
9	2.5	3.1	2.5	2.5	2.8	2.2	3.8
10	2.9	2.5	2.4	2.6	4.2	2.0	11.4
	$n = 42$	$n = 42$	$n = 42$	$n = 42$	$n = 42$	$n = 36$	$n = 12$
Extremely good set of teeth: 40 chews.							
1	1.9	2.0	2.3	2.1	3.7	3.2	—
2	3.5	3.9	4.0	3.0	4.2	3.7	—
3	4.4	4.4	4.3	3.4	3.8	3.1	—
4	58.0	60.0	57.5	38.1	40.7	36.7	—
5	26.6	27.1	26.9	22.1	19.5	17.7	—
6	11.3	10.7	12.1	11.4	6.9	6.7	—
7	4.6	5.2	6.1	4.6	2.9	3.6	—
8	2.2	2.9	4.2	2.4	0.94	1.7	—
9	0.77	0.98	0.94	0.82	0.41	0.48	—
10	0.56	0.56	0.97	0.54	0.17	0.83	—
	$n = 82$	$n = 82$	$n = 82$	$n = 82$	$n = 81$	$n = 46$	

Table 1 (cont.).

Fraction	Gelatin 10 %	Gelatin 15 %	Gelatin 20 %	Carrot	White of egg	Synthetic rubber	India- rubber
Bad set of teeth: 40 chews.							
1	0.62	0.66	0.68	0.72	2.3	1.1	--
2	1.4	1.3	1.4	1.2	2.7	1.4	--
3	2.2	2.0	2.0	1.5	3.0	1.7	--
4	37.6	35.3	33.5	17.0	38.7	26.1	--
5	26.6	24.9	25.9	14.9	22.6	18.1	--
6	16.8	15.9	16.1	11.5	12.3	12.2	--
7	10.0	10.5	10.2	8.9	6.5	7.9	--
8	5.4	6.3	5.9	5.6	3.6	4.9	--
9	2.8	2.8	3.5	3.2	1.5	2.5	--
10	2.0	3.2	3.9	5.3	0.97	2.8	--
	n = 84	n = 84	n = 84	n = 84	n = 82	n = 51	

reduction of the different materials from the figure series in the tables, there can hardly be any reason for commenting on these latter in more detail. The tables over the different material's degree of reduction are only given as a check, as subsequent calculations of volume, surface and mastication coefficient are based on them.

The average values for surface, volume and mastication coefficient calculated according to the method used in the investigation are given in Table 2.

The figures in the table show that, on the whole, white of egg and synthetic rubber are more easily reduced than any other of the tested materials. Carrot and formalin-hardened gelatin of varying gelatinous content agree well in reduction both for good and bad sets of teeth, and both when chewed at discretion as after 40 chews. When comparing the mastication coefficient for formalin-hardened gelatin, it is found that the higher the gelatinous content, the easier it seems to be to reduce the test portion to small pieces. With 20 per cent gelatin, the portion becomes harder but at the same time more brittle, which latter quality probably explains a higher mastication coefficient than might have been expected. The difference is nevertheless small. It can further be seen from the figures in the table that the mastication coefficient for indiarubber is considerably lower than for the other materials, a circumstance naturally due to the fact that indiarubber is very hard to chew.

TABLE 2.

Calculated surface, volume and surface area per c. cm. (mastication coefficient) for tests of different materials. The figures have been computed from the figures in Table 1. M. C. = mastication coefficient, sq. cm./c. cm.

Material	Surface, sq. cm.	Volume, c. cm.	M. C.
Extremely good set of teeth: Unrestricted number of chews.			
Gelatin 10 %	212.99	9.157	23.3
» 15 %	247.47	10.032	24.5
» 20 %	258.67	10.106	25.6
Carrot	188.21	7.971	23.6
White of egg	200.01	9.247	21.6
Synthetic rubber	223.27	7.933	28.0
Indiarubber	109.55	9.373	11.7
Bad set of teeth: Unrestricted number of chews.			
Gelatin 10 %	154.65	10.093	15.3
» 15 %	170.20	10.515	16.2
» 20 %	187.20	11.125	16.8
Carrot	141.06	8.567	16.5
White of egg	169.21	9.193	18.4
Synthetic rubber	177.36	9.059	19.6
Indiarubber	81.70	8.285	9.9
Extremely good set of teeth: 40 chews.			
Gelatin 10 %	228.28	9.543	23.9
» 15 %	241.52	10.058	24.0
» 20 %	252.75	10.764	23.5
Carrot	200.40	8.242	24.3
White of egg	242.27	7.966	30.4
Synthetic rubber	217.23	7.667	28.3
Bad set of teeth: 40 chews.			
Gelatin 10 %	167.71	10.193	16.5
» 15 %	168.70	10.612	15.9
» 20 %	174.11	11.098	15.7
Carrot	142.05	9.422	15.1
White of egg	209.57	9.125	23.0
Synthetic rubber	153.52	8.701	17.6

Finally, a smaller number of persons with good and poor sets of teeth have, in ways previously given, chewed the above tested materials, and each portion was fractionated twice. The purpose of the investigation was to compare the different materials with regard to the possibility of obtaining accordant values for the

same fraction by re-straining the test portion. The absolute and the percentual standard error for the strained fractions have been calculated from the differences. Some of the fractions have been made into one, as shown by the tables, to give more general figures. (See Table 3.).

The figures in the table show that both the values for the absolute standard error of measurement and also the variation coefficients (= standard error in per cent of the fraction's mean) are, for a good set of teeth, higher for carrot and white of egg compared with the corresponding values for gelatin. A comparison between gelatins of different concentrations reveals less pronounced differences. A comparison with corresponding figures for poor sets of teeth shows considerably lower standard errors. The differences in the standard error between different materials also become less, which may be due to the fact that reduction is less effective with poor sets of teeth. In spite of the amalgamation of some fractions, however, it is difficult to get a general survey of the figures. For this reason, Table 4 gives standard errors obtained from differences between calculated mastication coefficients.

Thus, mastication coefficients have been calculated for the two strainings of one and the same test portion, and in this table the coefficients have also been calculated for two consecutive tests with exactly 40 chews. From the differences, the standard error for a single determination has been calculated. The figures show clearly that 15 per cent gelatin gives throughout a smaller standard error than carrot, white of egg and synthetic rubber; this applies both to the absolute standard error and to the percentual error. An exception is synthetic rubber with a good set of teeth, when this material seems to be about as good as gelatin; it has, however, not been possible to get enough of the former for more thorough testing. Although the number of accomplished tests is not great, the figures nonetheless seem to indicate fairly definitely that 15 per cent gelatin should offer certain advantages.

*Summing up*, it may be said that the investigation verifies on the whole the assertions made at the theoretical discussion of the different materials. White of egg proves to be too easy to chew. This is, however, also true of synthetic rubber — a rather unexpected discovery, since the impression of a harder material is given during mastication. Carrot and gelatin seem about the

TABLE 3.

Standard error of measurement of a single determination, calculated on differences between two strainings of the same test with mastication at discretion and for both extremely good and bad sets of teeth. The standard error of measurement is calculated as standard deviation ( $=\sigma$ ), of a single determination on the one hand, as variation coefficient ( $=V$ ), i. e. in per cent of the pertaining mean, on the other.  $M$  = mean of the standard errors of the different fractions.  $n$  = number of persons.

Material	Standard error of measurement in straining; mastication at discretion						
	n		Fraction				M
			1—3	4—5	6—7	8—10	
Extremely good set of teeth.							
Gelatin 10 %	16	$\sigma$ V	0.302 3.7	5.62 7.1	1.25 8.1	0.637 16.1	1.95 8.8
„ 15 %	16	$\sigma$ V	0.158 1.6	3.96 5.0	1.16 7.1	0.530 13.8	1.45 6.9
„ 20 %	16	$\sigma$ V	0.350 3.2	8.53 10.5	1.57 10.7	0.707 17.4	2.79 10.5
Carrot	16	$\sigma$ V	0.408 4.0	4.96 7.5	2.86 15.6	1.22 25.8	2.36 13.2
White of egg	16	$\sigma$ V	0.664 8.7	4.68 7.8	2.72 14.2	1.58 13.8	2.41 11.1
Synthetic rubber	16	$\sigma$ V	0.504 5.2	2.25 4.9	1.89 19.1	0.500 28.6	1.29 14.5
Bad set of teeth.							
Gelatin 10 %	16	$\sigma$ V	0.167 6.6	3.19 5.8	1.85 6.8	1.19 9.6	1.60 7.2
„ 15 %	16	$\sigma$ V	0.178 5.6	5.85 9.5	2.14 7.5	1.50 12.4	2.42 8.8
„ 20 %	16	$\sigma$ V	0.228 5.7	4.03 5.5	1.75 5.7	0.901 7.8	1.73 6.2
Carrot	16	$\sigma$ V	0.321 7.7	5.80 13.3	3.68 14.7	1.80 16.1	2.90 13.0
White of egg	16	$\sigma$ V	0.273 5.4	3.81 9.0	1.70 9.8	1.00 7.9	1.70 8.0
Synthetic rubber	16	$\sigma$ V	0.179 4.2	2.20 4.2	1.80 9.2	0.285 4.2	1.12 5.5

TABLE 4.

Standard error of measurement of a single determination of the mastication coefficient, calculated on a series of differences between double strainings of the same test, and on double mastication tests (with 40 chews in each), carried out on a series of persons with both extremely good and bad sets of teeth. The standard error of measurement is given as standard deviation ( $=\sigma$ ) of a single determination, on the one hand, as variation coefficient ( $=V$ ), i. e. in per cent of the pertaining mean, on the other.

$n$  = number of persons.

Material	Standard error of measurement in straining (mastication at discretion)			Standard error of measurement in straining (40 chews)		
	$n$	$\sigma$	$V$	$n$	$\sigma$	$V$
Extremely good set of teeth.						
Gelatin 15 %	16	0.045	1.8	16	0.262	11.2
Carrot	16	0.097	3.9	16	0.350	13.6
White of egg	16	0.045	2.3	16	0.363	12.7
Synth. rubb.	16	0.073	2.4	13	0.263	8.2
Bad set of teeth.						
Gelatin 15 %	16	0.032	2.1	16	0.062	4.2
Carrot	16	0.075	4.5	16	0.211	14.7
White of egg	16	0.054	3.0	16	0.397	17.9
Synth. rubb.	16	0.044	2.4	15	0.110	6.5

same as regards chewing difficulty, but carrot (like white of egg) has a rather large error of measurement in straining, which is one of the reasons why it is less suitable. It does not matter very much which concentration of gelatin is chosen, as they all work out much the same when chewed. The author has decided on 15 per cent gelatin, as this content seems to be more suitable as regards consistency than the two others.



## Chapter 4.

### The preparation of test portions for chewing.

On the basis of the analysis which has been carried out on different materials 15 per cent formalin-hardened gelatin has been chosen as test material for subsequent investigations.

The portions were made by casting the prepared gelatin solution into rods, which were cut into pieces, hardened by formalin, and washed.

Gelatin leaf contains between 12—17 per cent of water, but this variation in content is probably of no importance. When making the gelatin solution, colouring matter and 5 per cent barium sulphate were added. It is difficult to distinguish and count uncoloured gelatin particles, on account of their transparency, and this is one of the reasons why barium sulphate is added: it makes the portions white and rather like sticks of shaving cream to look at. Anyhow, they do not look attractive to chew, so, to get over this, the solution is stained with fuchsin; this turns the finished portions pale pink like a Christmas sweet. There has also been another reason, though less important, for the addition of barium sulphate. As this salt has a high specific gravity, the particles get somewhat heavier from the addition, and this may prove of advantage in straining.

The gelatin solution was prepared as follows. The amount of water was measured out and coloured with a small quantity of fuchsin, after which all the gelatin powder was added at once. The mixture was then heated over a water-bath, stirring constantly, until the gelatin melted, care being taken that the temperature did not exceed 70—80° C. When all the gelatin had melted, barium sulphate was added; the latter should first be mixed with a little of the solution to form a thick paste and stirred until smooth. Still being stirred the finished mixture of gelatin + barium sulphate was poured into a number of metal containers all the same size. The heavy barium sulphate tends

to sink to the bottom, so one wants the solution to set as soon as possible; to this end, the metal containers are stood in water while being filled.

When the solution has set, the next question is how to get it out without damaging it. Now, the metal container consists of two cylinders, an outer and an inner one, the latter divided longitudinally into two halves. With a simple screwing device, the inner cylinder can be pushed up and taken apart. It goes without saying, that all the cylinders should be of exactly the same size, so that any of the inner ones fits any of the outer ones.

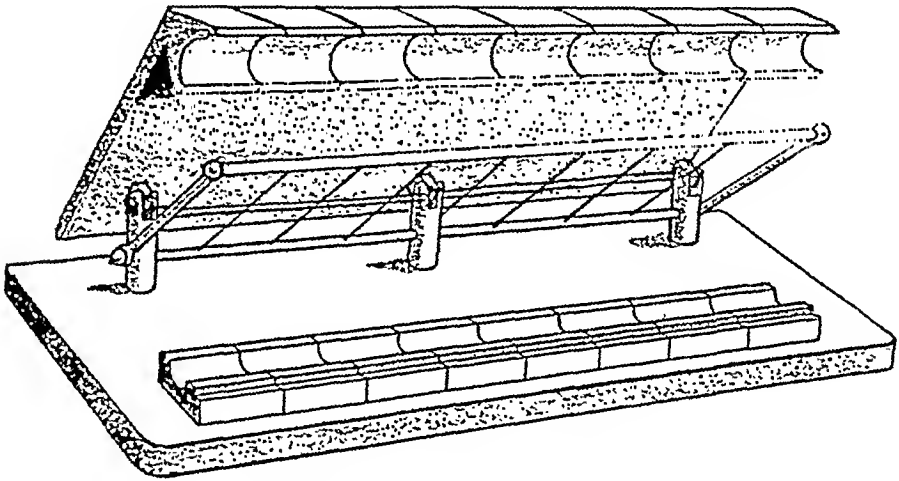


Fig. 1. The cutting machine.

Portions of fixed size are obtained by cutting the gelatin rod in two with a simple cutting-machine, consisting of two hinged metal blocks. When the blocks are shut together, a cylindrical space is formed of the same dimensions as the gelatin rod. The apparatus also has a fork with fine metal wires stretched at equal distances from one another. The gelatin rod to be cut is placed in the groove in the lower block and held there in position by the upper block. To cut, the frame of the fork, which rotates on a hinged joint, is raised. The metal wires run in tracks cut in the metal block. (Cf. Fig. 1.)

To try out the suitable size to be cut, so as to get a piece that is not too large to chew and that at the same time provides sufficient material for analysis, a number of persons were made to chew bits of varying sizes. The experiences obtained here were used to determine a certain size, which was afterwards used

in all tests with adults. Smaller pieces were used for children from 7—13 years of age. As mentioned in the review of the literature different authors have used test portions of different sizes. Of course the results obtained to a certain extent will be influenced by these sizes. In this investigation, however, no analysis has been made of this influence. The method of testing the mastication raises a number of questions, and it has been found necessary to limit the scope of the investigation in regard to this and some other problems. Except for children the same size of the test portions has been used throughout and this difference between children and adults has to be remembered in the following.

The cutting-machine is so constructed as to divide up the gelatin rod into 6 equal pieces. Each portion for adults is 23 mm. in diameter, and 22 mm. long, which corresponds to a volume of 934 c. mm. (The equivalent piece for children has a volume of 623 c. mm.) It should be mentioned that this value refers to the volume before hardening and washing: during these further operations the portion swells to a somewhat larger volume.

The weight and volume of the finished portions may vary for several reasons. The volume increase set up in connection with hardening and washing may not always be the same. The cutter does not always give pieces of exactly the same size, which may be due to the fact that, if the wires have become less taut, they do not cut through the cylindrical gelatin rod absolutely at right angles. This source of error can be controlled to a certain extent, however; a slack wire can be tightened up, and crookedly cut pieces discarded. Finally, there is always the possibility that the barium sulphate may, on account of its weight, have sunk before the gelatin set. This tendency in the former substance is, however, comparatively small, on account of the high viscosity of the gelatin. A simple method has been used to check how far this may be so: slices of equal thickness were cut from both ends of a rod, after which they were X-rayed beside one another. The barium sulphate appeared in the picture as small dots. Some differences in density could be observed between the pictures, but only very slight ones.

In order to discover how far the finished portions all remain the same *weight* as one another, 25 made with 15 per cent gelatin and 25 with 15 per cent gelatin + 5 per cent barium sulphate were weighed in a precision balance.

The average weight of a hardened and washed portion of gelatin only is 10.9 g. with a variation coefficient of 1.2 per cent. The corresponding value for gelatin with barium sulphate is 11.4 g. with the same variation coefficient, i. e. 1.2 per cent. The portions used for children weighed 7.96 g., and had a variation coefficient of 0.41 per cent. The variability found can be considered of no importance; and the weight can be said to show good constancy.

A number of variations in weight are due to errors in weighing. A series of pieces were weighed twice to give an idea of how far this is so. These double weighings gave a variation coefficient of  $\pm 0.18$  per cent for gelatin only, and  $\pm 0.28$  per cent for gelatin with barium sulphate. The low figure shows that only a small part of the weight variation is due to errors in weighing, as might be expected, since precision scales are used. The main variation is plainly due to the fact that the pieces vary somewhat in size.

In order to get a further orientation, the *volume* of hardened and washed test portions was also determined. In 25 pieces of 15 per cent gelatin only, the average volume was found to be 10.1 c. cm. with a variation coefficient of 1.5 per cent. The corresponding values for 15 per cent gelatin with 5 per cent barium sulphate was 10.6 c. cm. and 3.5 per cent. For children, pieces with a volume of 7.1 c. cm. and a variation coefficient of 1.1 per cent were used. It was established by double determinations of the volume that the error of measurement for pieces with barium sulphate is 0.5 per cent, and for pieces without it, 0.9 per cent. Some part of the greater variation of the former compared with that of the latter can probably be ascribed to the uncertainty attached to the method for determining volume, but the difference cannot wholly be explained by the greater error of measurement. The investigation shows, however, that pieces of 15 per cent gelatin and those of 15 per cent gelatin + 5 per cent barium sulphate are both satisfactorily constant as regards volume and weight.

Before the pieces of gelatin are ready for use in mastication tests, they must be *hardened* in formalin, and the formaldehyde afterwards removed, so that they are not unpleasant to chew. The gelatin becomes harder in consistency and, most important of all, insoluble in water.

The formalin's content of formaldehyde varies between 36 and 38 per cent, so that the concentration of the diluted solution used for hardening varies between 4.15 per cent and 4.75 per cent. This

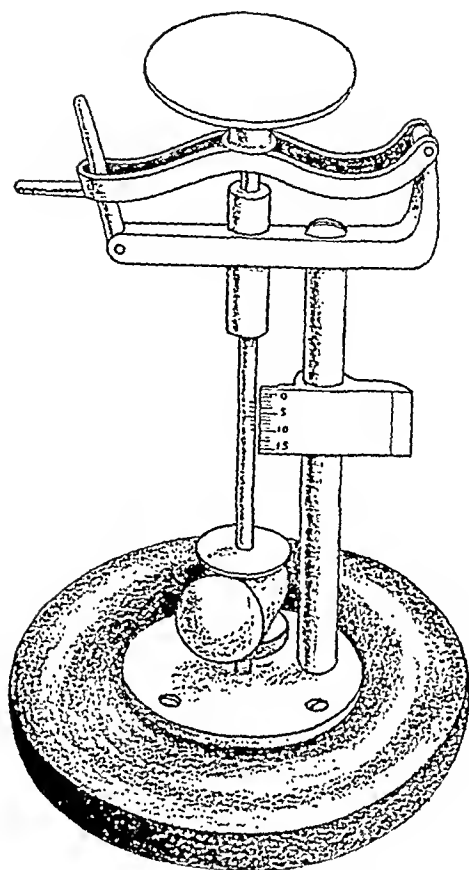


Fig. 2. Apparatus for measuring compressibility of gelatin.

variation constitutes a source of error, which is difficult to avoid in practice, so that it is of importance that the hardening procedure is in other respects as standardized as possible, to exclude further sources of error.

During hardening the test portions were kept in bottles with patent stoppers. The time taken was 24 hours, 50 test portions being hardened with 50 c. cm. of formalin, diluted with 350 c. cm. of water. After this it remains to treat the pieces so as to render them pleasant to chew; this is done by washing in running water. A rubber tube brings water from the tap into the bottom of the vessel where the pieces are. After 12 hours' rinsing, they have a completely indifferent taste.

As has already been said in the general discussion of gelatin as a test material, this substance has the advantage of varying as regards gelatin content and hardening. In the first place,

then, pieces with different content can be tested, and also pieces of different hardness. In the latter case, both the strength of the hardening solution and the time for its action can be varied.

The portions to be chewed are tested with a special apparatus which measures their compression under an increasing load. (Cf. Fig 2.) The apparatus has a plate which can be raised and lowered, and which has a groove in which the piece of gelatin lies firm. The gelatin is compressed by weights via a transforming device provided with a Vernier scale. The latter makes it possible to determine the compression at a certain load to  $\frac{1}{10}$  of a millimetre. The resistance of the test portion to pressure can also be determined by the same apparatus. The set-up is the same, with the difference that the plate with which the portion is compressed is replaced by a blunt point 4 mm. in diameter. When the load reaches a sufficient height, the test portion splits into two halves.

#### *Properties of the test material.*

To get some idea of the properties of the test material, it has been investigated with reference to compressibility and resistance at different loads. It has been interesting to compare in these respects pieces of different gelatin content, some hardened in standardized wise, some hardened for longer or shorter periods with stronger or weaker solutions. It has also been of interest to investigate how far the material remains constant when kept.

A series of test portions has been tested with the apparatus described above, and the results are given in table 5. The numerical results here obtained give the compressibility expressed in millimetres at a load expressed in grammes.

It is now possible in the first place to make a comparison between the compressibility of pieces of different gelatin content hardened for the same time with the same hardening, and tested immediately after washing. It is found that the compressibility in tests with increasing loads from 200—1500 g. gets less with raised gelatin content. Thus, pieces of 10, 15 and 20 per cent gelatin with barium sulphate are, at a load of 1500 g., compressed about 3, 1.5 and 1 per cent of their diameter respectively. For these tests, the cylinder-shaped pieces are in a horizontal position. The variation is comparatively small, which means that the pieces are all alike. For 15 per cent gelatin with barium sulphate the value for the variation coefficient (= standard deviation expressed in per cent of the mean) is 3—5 per cent at different loads.

In a comparison between 10 and 15 per cent gelatin + barium sul-

TABLE 5.

Test pieces examined with regard to compression.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.  $V$  = variation coefficient.

Load, g.	$M \pm \epsilon(M)$	$\sigma$	$V$	Remarks
10 % gelatin + 5 % BaSO <sub>4</sub>				
200	$1.734 \pm 0.022$	0.158	9.1	Test carried out immediately. Hardening during 24 hours in 50/350 formalin solution. 50 tests.
500	$3.212 \pm 0.030$	0.213	6.6	
1000	$4.984 \pm 0.027$	0.190	3.8	
1500	$6.164 \pm 0.031$	0.220	3.6	
200	$1.796 \pm 0.013$	0.089	5.0	Test carried out after 4 days. Hardening during 24 hours in 50/350 formalin solution. 50 tests.
500	$3.380 \pm 0.019$	0.137	4.1	
1000	$5.218 \pm 0.021$	0.151	2.9	
1500	$6.421 \pm 0.018$	0.127	2.0	
15 % gelatin				
200	$0.520 \pm 0.006$	0.010	7.7	Test carried out immediately. Hardening during 24 hours in 50/350 formalin solution. 50 tests.
500	$1.000 \pm 0.010$	0.072	4.5	
1000	$2.746 \pm 0.011$	0.075	2.7	
1500	$3.726 \pm 0.013$	0.091	2.4	
15 % gelatin + 5 % BaSO <sub>4</sub>				
200	$0.508 \pm 0.001$	0.027	5.3	Test carried out immediately. Hardening during 24 hours in 50/350 formalin solution. 50 tests.
500	$1.428 \pm 0.010$	0.072	5.1	
1000	$2.502 \pm 0.012$	0.088	3.5	
1500	$3.420 \pm 0.013$	0.092	2.7	
200	$0.696 \pm 0.007$	0.033	7.6	Test carried out after 4 days. Hardening during 24 hours in 50/350 formalin solution. 50 tests.
500	$1.610 \pm 0.010$	0.070	4.3	
1000	$2.688 \pm 0.011$	0.079	2.9	
1500	$3.630 \pm 0.014$	0.096	2.7	
200	$1.200 \pm 0.016$	0.082	6.8	Test carried out immediately. Hardening during 12 hours in 50/350 formalin solution. 25 tests.
500	$2.304 \pm 0.019$	0.093	4.1	
1000	$3.788 \pm 0.024$	0.120	3.2	
1500	$4.932 \pm 0.019$	0.095	1.9	
200	$0.580 \pm 0.012$	0.058	10.0	Test carried out immediately. Hardening during 48 hours in 50/350 formalin solution. 25 tests.
500	$1.432 \pm 0.014$	0.069	4.8	
1000	$2.432 \pm 0.019$	0.095	3.9	
1500	$3.264 \pm 0.016$	0.081	2.5	
200	$1.096 \pm 0.015$	0.073	6.7	Test carried out immediately. Hardening during 24 hours in 25/350 formalin solution. 25 tests.
500	$2.304 \pm 0.021$	0.106	4.6	
1000	$3.888 \pm 0.039$	0.196	5.1	
1500	$5.128 \pm 0.013$	0.215	4.2	

Table 5 (cont.)

Load, g.	$M \pm \varepsilon(M)$	$\sigma$	$V$	R e m a r k s
200	$0.312 \pm 0.009$	0.044	14.1	Test carried out immediately. Harde- ning during 24 hours in 100/350 for- malin solution. 25 tests.
500	$0.872 \pm 0.012$	0.061	7.0	
1000	$1.628 \pm 0.019$	0.093	5.8	
1500	$2.172 \pm 0.019$	0.094	4.3	
20 % gelatin + 5 % BaSO <sub>4</sub>				
200	$0.300 \pm 0$	0	0	Test carried out immediately. Harde- ning during 24 hours in 50/350 for- malin solution. 50 tests.
500	$0.754 \pm 0.011$	0.079	12.2	
1000	$1.560 \pm 0.018$	0.125	8.0	
1500	$2.106 \pm 0.016$	0.110	5.2	
200	$0.428 \pm 0.006$	0.045	10.5	Test carried out after 4 days. Harde- ning during 24 hours in 50/350 for- malin solution. 50 tests.
500	$0.924 \pm 0.008$	0.058	6.3	
1000	$1.774 \pm 0.012$	0.082	4.6	
1500	$2.356 \pm 0.014$	0.096	4.1	

phate we find the differences at different loads fairly small. They are nevertheless statistically significant, and increase from an average of 1.2 to 2.7 mm., constituting about 0.5 to 1 per cent of the diameter of the test piece. The differences between 15 and 20 per cent gelatin with barium sulphate, though statistically significant, are even less, being on an average 0.1—0.5 per cent of the diameter.

To investigate how far the addition of barium sulphate affects the test material, pieces of 15 per cent gelatin only have been tested and compared with 15 per cent gelatin + barium sulphate. The difference in compressibility at rising loads is very small, and when the load is 1500 g. the difference is only about 0.1 per cent of the piece's diameter.

Gelatin of different content was tested after having been kept 4 days, and a comparison with the results obtained after testing fresh pieces showed extremely small, though statistically significant, differences, indicating that the compressibility increases with keeping.

In hardening, a period of 24 hours with 50 parts of formalin and 350 parts of water has been used as standard method. A comparison shows that a hardening time of 12 hours gives softer pieces, and one of 48 hours harder pieces, than this. Differences at a load of 1500 g. between a hardening of 12 and of 24 hours are 10 times greater than the difference between one of 24 and of 48 hours. In the latter case, the difference is only  $0.156 \pm 0.021$  mm.

Finally, 15 per cent gelatin with barium sulphate is tested after hardening, with 25 and 100 parts of formalin to 350 parts of water. Comparing the values with those obtained for standard-hardened gelatin of the same content, it is found that, at a load of 1500 g., the mild hardening gives



TABLE 6.

Test pieces, examined with regard to resistance by loading.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.  $V$  = variation coefficient.

Number of tests	Bursting point, kg.			Time of test after washing	Hardening, hours	Concentration of formalin
	$M \pm \epsilon M$	$\sigma$	$V$			
10 % gelatin + 5 % $\text{BaSO}_4$						
25	$0.332 \pm 0.023$	0.114	12.5	Immediately	24	50/350
25	$1.010 \pm 0.036$	0.189	17.3	After 4 days	,	,
15 % gelatin						
25	$1.110 \pm 0.018$	0.091	8.0	Immediately	24	50/350
15 % gelatin + 5 % $\text{BaSO}_4$						
25	$1.195 \pm 0.032$	0.162	13.5	Immediately	12	50/350
25	$1.252 \pm 0.016$	0.082	6.6	,	24	,
25	$1.276 \pm 0.026$	0.139	10.2	,	48	,
25	$1.452 \pm 0.013$	0.065	4.5	After 4 days	24	,
25	$1.140 \pm 0.028$	0.141	12.4	Immediately	,	25/350
25	$1.776 \pm 0.026$	0.120	7.5	,	,	100/350
20 % gelatin + 5 % $\text{BaSO}_4$						
25	$1.861 \pm 0.011$	0.057	3.1	Immediately	24	50/350
25	$1.828 \pm 0.016$	0.079	4.3	After 4 days	,	,

softer pieces with a difference of  $1.768 \pm 0.015$  mm., and the stronger one gives harder pieces with a difference of  $1.218 \pm 0.023$  mm. It is further found that mildly hardened 15 per cent gelatin agrees fairly well with 10 per cent gelatin hardened according to the standard method and also that strongly hardened 15 per cent gelatin shows about the same values as 20 per cent standard-hardened gelatin.

The test material has up to now been discussed with reference to compressibility. Table 6 gives the values for the load which causes the test piece to split into two halves.

A comparison between 10, 15 and 20 per cent gelatin with barium sulphate, hardened for an equally long time with equally strong solution (standard hardening) and tested immediately after washing, shows that the resistance increases with the gelatin content. Thus, twice the load, on an average 1.861 kg., is required to split a piece of 20 per cent gelatin content compared with one of 10 per cent. The resistance of 15 per cent gelatin is nearer that of 10 per cent gelatin; this is shown by the fact that the difference between 10 and 15 per cent gelatin is  $0.320 \pm 0.028$  kg., and between 15—20 per cent gelatin it is  $0.612 \pm 0.023$  kg.



## Division of the test portion into fractions by straining.

In the first experiments of the author to sort out the particles of the chewed portion into fractions, an apparatus was used that had a spray placed above the strainers. A device driven by an electrical motor moved the strainers horizontally backwards and forwards. But the apparatus was fragile, and troublesome to manage. The sluicing of the strainers proved uneven, as a number of particles blocked the holes, in spite of the shaking, and thus impeded the flow of water.

### *The apparatus.*

The experiences gained from this apparatus were used in constructing another one, sturdier and more easier to manage, where the particles did not block the holes in the same way. This apparatus consists of 10 strainers, which can be pushed in from the side into a metal cylinder, through openings exactly adapted for this purpose, and can then be fixed in this position. Beside the metal cylinder there is a two-branched water-pipe and an inlet pipe from either branch is joined to each of the strainer pockets, to which water is thus brought direct. The branched pipe continues in two, 1.5 m. long main-pipes of glass, and in its lower part it has a water-distributing tap. Finally, the strainers have a side outlet in the form of a pipe the same height as the metal cylinder. In this way the rate of flow in all pipes to the strainers will be equal. (Cf. Figure 3.)

As the water is introduced from the side in each strainer, the whole system is washed through by a column in spiral rotation. The particles are sucked downwards towards the next strainer, and a number pass through, while others are stopped by the strainer, to be caught up in the flow of water again and make another attempt to get through. By repeating this sufficiently often, practically all the particles that can pass through, do so.



It is possible, with the above-mentioned distributing-tap, to change the direction of the flow in the strainers, so that the column of water rotates now clockwise, now anti-clockwise. The tap can be set both in active position, when the water passes through either of the branches, and in neutral position, when the flow is stopped. In the latter position, the column of water sinks; the vortices are thereby increased and the particles are drawn downwards through the holes of the strainer. After a fixed number of seconds, the tap is turned back into the active position, the water spurts forth in the other shank of the pipe and the course of events is repeated, but with the column of water now rotating in the opposite direction.

The method of straining must be standardized as far as possible, in order to give comparable results. A stop-watch is used to ensure that a certain total time for straining is used, and also to check the time for the reversing of the jet of water. The water pressure must also be kept constant.

Under the circumstances which have been tested, the pressure of the water-system has proved to be fairly constant. When the tap in the supply pipe has been set to give the desired pressure, it does not as a rule need any further alteration, but this does not do away with the necessity of a certain control. Such control is easily carried out with the help of the water columns in the glass pipes.

These pipes are also a gauge of the precision with which the straining apparatus has been made, since the height of the water column in the parallel pipes will only be the same provided that the branched pipe and the inlet pipes on both the right and the left side have exactly the same dimensions. Thus, it needs no more than that a particle should be squeezed into one of the twenty inlets and there impede the passage of the water, for a distinct difference to arise in the level of the columns of water in the two branches.

To be used for mass investigations, the straining apparatus must, of course, be fairly easy to manage. The strainers are mounted in such a way as to be easy of access, and can quickly be taken out of the metal cylinder, emptied, and replaced. When removing and replacing the strainers, the tap is in the neutral position, so that the water pressure does not have to be regulated between each straining. It should be emphasized that the not inconsiderable lasting qualities of the apparatus have been

attained by its having only one movable part, namely the distributing tap.

In the apparatus, the diameter of the smallest hole is 1 mm., and increases by 1 mm. for each strainer in an arithmetical series up to 10 mm. for the largest holes. Yet another strainer, with holes  $\frac{1}{2}$  mm. in diameter, has been used in a small number of strainings. It was introduced at the very bottom of the apparatus to control how much got through the 1 mm. strainer. The fraction collected on the  $\frac{1}{2}$  mm. strainer was found to be extremely small. 75 test portions were strained. Several of these yielded an amount impossible to measure in the  $\frac{1}{2}$  mm. strainer. On an average  $0.0368 \pm 0.0091$  c. cm. collected on the strainer, i. e. a volume of not quite 0.1 c. mm. of very small particles.

In the determination of the size of the different fractions, the number of particles are counted in those from the less fine and the coarse strainers with holes 4—10 mm. in diameter. The determination of the three finest fractions, where the holes have a diameter of 1—3 mm. is made by measuring the volume after sedimentation in graduated glass tubes, since counting was found to take too much time. To get the volume, the contents of the strainer is emptied into a funnel filled with water, the particles rapidly sinking to the bottom of a graduated tube fixed under the funnel. Before reading off the volume, the particles should be shaken down until the volume remains constant. The device used, which is both simple and effective, consists of a spring which rests against an eccentric-disc, driven by a motor. If the graduated tube is pressed against the plate in such a way as to be affected from the side by the latter's vibrations, it can be seen how the particles are shaken down and the volume quickly sinks to a constant value.

### *Pressure, rate of reversing and time.*

In using the straining apparatus, it is possible, as has been said in Chapter 2, for certain factors to vary during straining, namely pressure, rate of reversing and the time taken. The question has been to find the combination of these three at which the apparatus gives the best results. A number of persons have chewed pieces of constant size and composition, after which double determinations were carried out in series of 30 tests, the same portion being strained twice. Table 7 shows that pressure,

TABLE 7.

Standard error of measurement for the mastication coefficient computed from differences between 2 strainings of a number of tests during different conditions.  $n$  = number of tests (each with 2 determinations).  $\sigma_i$  = standard error of measurement for a single straining.  $V$  = standard error in per cent of the corresponding mean.

Pressure	Time	Revision	$n$	$\sigma_i$	$V$
1. Highest	longest	slowest	30	0.017	0.9
5. " "	long	slow	30	0.023	1.1
3. High	longest	"	30	0.032	1.9
6. " "	"	slowest	30	0.044	1.9
4. Highest	long	"	30	0.037	2.0
8. High	short	slow	30	0.030	2.0
2. " "	long	slowest	49	0.035	2.1
10. Low	"	slow	30	0.033	2.1
13. " "	short	short	30	0.047	2.1
11. High	"	"	30	0.062	2.6
12. " "	long	immediate	29	0.060	2.6
7. " "	"	slow	30	0.045	2.8
15. " "	"	short	30	0.033	3.6
14. Low	"	"	29	0.078	3.7
9. Highest	longest	slow	30	0.065	3.9
16. Low	long	immediate	26	0.036	4.2
17. " "	short	slow	30	0.101	4.9

time for straining and reversing were tested in 17 combinations. The error in measurement for a single determination of the mastication coefficient has been calculated for each combination.

The different combinations are arranged in the table in a progressive series according to the percentual size of the standard error.

We shall first discuss the *pressure*. The figures show that low pressure is inferior to both high pressure and the greatest pressure, even though it may, in combination with a long period of time, give a standard error of only 2.1 per cent. In a comparison between high pressure and the greatest pressure, the latter is found to give a somewhat lower standard error in long or maximal periods of time. On the whole, then, the highest pressure is to be preferred.

Higher values for the error in measurement are found in immediate and short *reversing* than in slow and slowest reversing. Under otherwise similar conditions, the latter must be the best.

It now remains to test the *time* taken in straining. A short

time of 3 minutes gives a higher standard error than long or the longest time. If we compare these latter times, i. e. a straining time of 6 and 12 minutes, we find better values for 12 minutes.

As the table shows, the highest standard error is given by low pressure, short time, and slow or immediate reversing, it then amounting to between 4 and 5 per cent. As regards the standard error, it would naturally be wisest to chose the combination of highest pressure, slowest reversing and maximal time, which gives a standard error of only 0.9 per cent. However, from a practical point of view, another combination is preferable, namely high pressure, long time and slowest reversing. The highest pressure means that the water is to a relatively large extent squeezed out through leaks in the apparatus. The longest time makes the determination take nearly twice as long as it otherwise would. For these reasons, the author has chosen the second combination mentioned above. The standard error for this combination amounts to  $2.1 \pm 0.21$  per cent, and is probably at a level to ensure satisfactory reliability of the method. To get a somewhat more exact idea of the standard error of the method, a larger number of determinations have been made for this combination than for others, namely 49. It should, incidentally, be pointed out that the differences between different combinations are to a certain extent conditioned by chance, due to the number of determinations not being very large.

The difference due to the error of measurement is of no very great importance when we consider that, in determining the mastication coefficient for an individual, we have to reckon with a not inconsiderable variation on account of the subject in question not always chewing in the same way, which causes differences between two tests. We have therefore considered ourselves justified in choosing a method which has advantages from the point of view of saving work, although its standard error is somewhat larger than the one characterizing a lengthy and more troublesome straining method.

As standard method, then we have chosen high pressure (100 cm.), longest reversing (12 seconds) and long straining time (48 seconds). The straining goes on in this way for 6 minutes. This method has a standard error of measurement in straining of about 2 per cent.



## Testing of the test portion's calculated surface and volume.

In the theoretical discussion in Chapter 2 as to the way of calculating the surface and volume for the fractioned test portion, formulas were given on the assumption that the particles in the fractions correspond on an average to cubes and octahedrons respectively.

The calculations demand obtaining for the finer fractions — when the volume of these is known — the value of the number of particles in 1 c.cm. of sedimented volume. The particles in 20 c.cm. volume, measured out for each one of the finer fractions, were counted. The mean number of particles to 1 c.cm. in fractions where the strainer-holes were 1 mm. in diameter, was 545, in fractions with 2 mm. diameter 138, and in fractions with 3 mm. diameter 49.

From the above-mentioned formulas, it is possible to work out coefficients with which the volume of the different fractions can easily be calculated. The volume of the test portion is obtained by multiplying for fractions 1—3 their volume, and for fractions 4—10 the number of particles, by the respective coefficients. The values for the calculated coefficients are given in Table 8.

Coefficients for calculating the total surface of the test portion, drawn up on the same assumptions as in the calculation of its volume, are also given in Table 8.

Now, when the assumptions made render it possible to calculate the extent of the test portion's volume and surface, a simple expression for the degree of reduction can also be got by computing surface per volume unit. The value then obtained is called here the *mastication coefficient* for the reduction of the portion. The calculated volume and surface do not necessarily correspond to the actual ones, but then the calculated values should differ in the same direction from the actual ones. If, by

TABLE 8.

Coefficients for calculation of volume and surface. It is assumed that the particles in fractions 10—4 correspond to cubes and the particles in fractions 3—1 to octahedrons.

Number of fraction									
1	2	3	4	5	6	7	8	9	10
Coefficients for calculation of volume									
303.97	362.87	348.75	32.22	58.83	97.11	149.18	217.16	303.17	409.34
Coefficients for calculation of surface									
2139.33	1506.75	1035.33	60.75	90.75	126.75	168.75	216.75	270.75	330.75

assuming that the particles have the form of octahedrons, too low a value is obtained for the volume, the values for the surface ought also to be too low, and in the same way, if a calculation assuming the form of cubes gives too high a value for the volume, the value for the surface should also be somewhat too high. In calculating the mastication coefficient therefore, it is more correct to relate the calculated surface to the calculated volume than to relate it to the known volume. This procedure has consequently been followed throughout.

Table 9 gives the average values for calculated surface and volume for grown-up men and women whose sets of teeth are extremely good, good, bad, and extremely bad.<sup>3</sup> The test subjects chewed standardized portions until they felt ready to swallow.

The calculations show that if we assume the particles to correspond on an average to cubes with a side diagonal half-way between the diameter of strainer-holes letting the particles through and that of those that do not, the value obtained for the calculated volume is too high compared with that of the actual volume; the values agree rather better, however, when the fractions are large on the coarse strainers and small on the finer ones, as is the case with extremely poor sets of teeth. In the opposite case — with good sets of teeth — with large fractions on the finer strainers, larger values are obtained for the calculated volume compared with the actual one. The deviations can be 35—40 per cent. It therefore seems as if the assumption

<sup>3</sup> A closer definition of what is implied here by extremely good, good etc. sets of teeth will be given further on in this paper.

TABLE 9.

Mastication coefficient calculated from figures for surface and volume determined on the basis of means of the fractions for men with extremely good sets of teeth (63 persons), good sets of teeth (60 persons), bad sets of teeth (51 persons) and extremely bad sets of teeth (55 persons), and on the basis of means of the fractions for women with extremely good sets of teeth (61 persons), good sets of teeth (76 persons), bad sets of teeth (50 persons) and extremely bad sets of teeth (50 persons). M. C. = mastication coefficient, sq. cm./c. cm.

Set of teeth	Assumed shape of particles at calculation								
	Cube 1—10			Octahedron 1—3, cube 4—10			Octahedron 1—10		
	Surface, sq. cm.	Volume, c. cm.	M. C.	Surface, sq. cm.	Volume, c. cm.	M. C.	Surface, sq. cm.	Volume, c. cm.	M. C.
M e n									
Group I, extremely good	363.92	14.665	24.8	252.44	10.553	23.9	210.09	6.913	30.4
> II, good	276.85	14.086	19.7	214.49	11.647	18.4	159.82	6.640	24.1
> II, bad	229.44	13.185	17.4	188.36	11.556	16.3	132.45	6.215	21.3
> IV, extremely bad	218.44	12.945	16.9	180.25	11.457	15.7	126.11	6.102	20.7
W o m e n									
Group I, extremely good	347.16	13.934	24.9	241.67	10.094	23.9	200.42	6.569	30.5
> II, good	284.87	13.329	21.4	211.21	10.552	20.0	164.45	6.283	26.2
> III, bad	244.75	12.879	19.0	191.36	10.826	17.7	141.30	6.071	23.3
> IV, extremely bad	228.30	12.566	18.2	183.41	10.832	16.9	131.30	5.924	22.2

that the particles are, on an average, cube-shaped, only applies to the not so fine and the coarse fractions with fairly large particles.

If, on the other hand, calculations are carried out on the assumption that the particles correspond on the whole to octahedrons, where, if the base diagonal is the same size as the cube's side diagonal, the volume of the former will be less than that of the latter, the values obtained for the test portion's calculated volume are throughout smaller than the actual volume. The deviations are 30—40 per cent. They seem to be somewhat less when the fractions on the fine strainers are large, i. e. with good sets of teeth, compared with bad sets, when the fractions in the fine strainers are small. On closer inspection of the shape of the particles in a test portion, they seem, further, to be preponder-

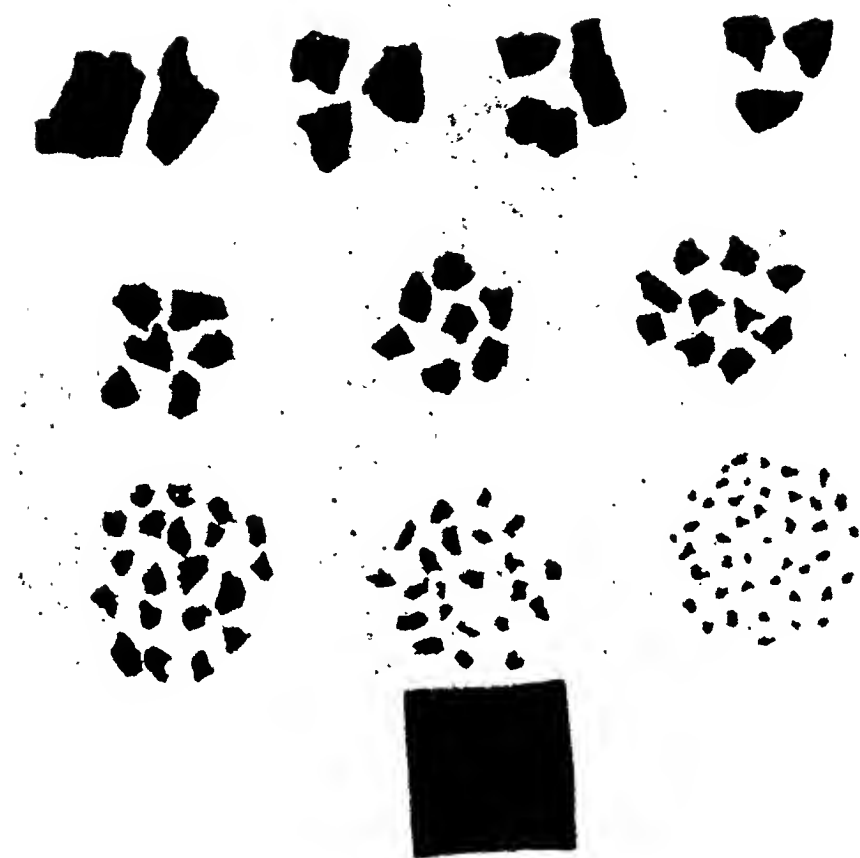


Fig. 4. Samples in nearly natural size of the different fractions and a test portion.

atingly pointedly oval in form in the finer fractions, and more rounded in the less fine and coarse ones. (Cf. Figure 4.) Actually, the calculated and actual volumes are found to tally very well if the calculations are made with octahedrons for the fractions for strainers 1—3, and with cubes for those 4—10. With a view to getting an idea of the deviations between the real values and the computed figures the differences between these have been calculated for 229 men and 237 women. It has been found that for women there is no appreciable mean deviation. The mean of the differences is  $0.86 \pm 0.65$  per cent. For men the corresponding figure is  $6.6 \pm 0.76$  per cent. The computed volume is somewhat greater

than the real. Of special interest is the fact that the standard deviation for men is 11.6 per cent and for women 10 per cent. This signifies that sometimes quite large deviations between the computed and the real values may arise.

Table 9 also gives the values for the mastication coefficient calculated from the average surface per volume unit. It may be of interest to compare the values obtained in calculations made on different assumptions. The highest values for the mastication coefficient are found in calculations assuming that the particles correspond throughout to octahedrons, and the lowest values in those where cubes and octahedrons have been combined. The table shows, further, that the coefficient gets less as the sets of teeth get worse. For a closer comparison of the coefficients for varying sets of teeth, however, readers are referred to the latter part of this work.

### *Control by weighing.*

It is now possible to get a further control for the calculations of the test portion's volume. The fractions are weighed, and from the weights is calculated — when the specific gravity is known — the volume for each fraction. Still using the same test portion, a calculation, based on the number of particles and the measured sedimented volume, is made of the volume of the different fractions.

An investigation of this kind has been carried out on 10 test portions. Table 10 gives, for purposes of comparison, figures which have been calculated both from the weight of the portion and also from the number of particles and the sedimented volume.

The figures in the table show us that there is good accordance between volume calculated from the weight of the test portion, and volume calculated on the assumption that the particles in fractions 1—3 correspond to octahedrons, those in fractions 4—10 to cubes. The average difference is  $0.30 \pm 0.10$  c. cm. or  $3.04 \pm 1.01$  per cent. A corresponding comparison on the assumption that the particles in all the fractions are in the form of cubes shows throughout higher values, with an average difference of  $2.40 \pm 0.20$  c. cm. or  $24.0 \pm 2.0$  per cent, and on the assumption that they have the form of octahedrons, the values are lower throughout, with an average difference of  $4.14 \pm 0.15$  c. cm. or  $41.5 \pm 1.5$  per cent.

TABLE 10.

Volume calculated from weight and number of particles of fractions of 10 tests.

Test	Weight, g.	Volume calculated from weight, c. cm.	Volume calculated from number of particles		
			Cube 1-10	Octahedron 1-3, cube 4-10	Octahedron 1-10
I	11.37	10.57	12.91	10.73	6.09
II	10.83	10.07	12.80	10.40	6.03
III	9.51	8.84	12.02	9.13	5.67
IV	10.73	9.98	12.01	9.90	5.66
V	12.17	11.32	13.67	12.00	6.45
VI	10.30	9.58	11.76	10.21	5.54
VII	10.07	9.36	11.50	9.90	5.42
VIII	10.31	9.59	10.68	9.24	5.04
IX	10.73	9.98	13.24	10.53	6.24
X	11.11	10.33	12.98	10.61	6.12

By weighing the particle mass and calculating the volume for the last three fractions, we can get an idea of how much of the measured volume consists of water. A calculation has been carried out on 10 test portions; the average amount of water in 1 c. cm. for fractions remaining in the strainer with holes of 1 mm. in diameter is found to be 50.6 per cent, for fractions with strainer-holes 2 mm. in diameter 50.7 per cent and for fractions with strainer-holes 3 mm. in diameter 50.3 per cent. A calculation of the amount of water made from the measured, sedimented volume on the assumption that the particles are in the form of cubes, gives 35 per cent, 23 per cent and 26 per cent respectively. The same calculation assuming the particles to correspond to octahedrons gives 69 per cent, 64 per cent and 65 per cent respectively. It is probably true that the volume values, calculated from the weight of the fractions are somewhat higher than the true values, since there is no doubt a certain amount of water in the weight obtained. (The particles were dried with the help of filter paper, and this drying is sure not to be completely effective.) For this reason the percentage values calculated from the weight are very likely too low. The real values for the average content of water should therefore lie quite near those obtained from the sedimented volumes on the assumption that the particles correspond, on the whole, to octahedrons.

*Colorimetric control.*

We have now shown that the volume of the test portion to be chewed can be determined direct by weighing, and that the values obtained agree with the values calculated from the number of particles and the measured, sedimented volume after fractionation. We have further shown that the calculated volume agrees with the actual one of the test portion. The portion's surface is now calculated from the same fractions as its volume was, and we should therefore be able to expect the calculated surface to agree fairly well with the actual one. Nevertheless, it would be a good thing if the surface could also be determined direct, without previous fractionation, in order to check the calculated values in the same way. It should be possible to gauge the total surface of the portion by treating it with a suitable chemical, which can be absorbed, and which has the further property of being removable again and able to undergo a quantitative analysis. At the suggestion of Professor TORSTEN TEORELL, the author has tried out a method which consists in staining the test portion with a water-soluble, colloidal dye and, after washing out of the latter, the photometric determination of the intensity of colour in the solvent.

In the first experiments, a water-soluble dye, *Nachtblau*, was tested. The colour of the fluid was read off on a Pulfrich (Zeiss) photometer of usual construction. After trying out the dye concentration most suited for reading off on the photometric scale used, a concentration of 1 promille was chosen as standard colouring-fluid. A number of thin slices of formalin-hardened gelatin with known surface-volume (10.92 sq. cm.) were coloured with equal quantities of the fluid. The experiments showed that the values read off gave a higher colour intensity in the fluid after the colouring process than before it. Further, the photometer gave a larger reading after colouring a bigger gelatin surface than after colouring a small one. A microscopic investigation of the colouring-fluid after use revealed that a precipitation of colouring grains takes place during use, and this explains the above-mentioned rise of the values read off from the apparatus. Formalin-hardened gelatin has an acid reaction, and as this might possibly produce the precipitation, the experiment was made of adding weak acid to the colouring-fluid. Microscopic investigation showed precipitation. Weak alkali was now added to the fluid instead





TABLE 11.

Photometer figures, corresponding to different number of gelatin disks with a surface of 10.92 sq. cm.

Number of disks	Surface, sq. mm.	Photometer figures
6	6552	330
12	13104	470
18	19656	530
24	26208	570

polation, to calculate the surface corresponding to a certain reading on the photometer.

Aided by the figures obtained in this way, 16 further test portions were investigated; in the first place in that surface and volume were calculated on the basis of the values obtained when the respective portions were strained, in the second place in that the portions were coloured and the surface determined with a photometer. The values obtained are shown in Table 12.

It is found that the separate values admittedly show deviations, but that, on the whole, they agree pretty well.

TABLE 12.

Surface and mastication coefficients (M. C.), calculated on the basis of straining and on the basis of colour determination of 16 tests.

Test	Calculated volume, c. cm.	Calculated surface, sq. cm.	M. C.	Colouredetermined surface, sq. cm.	M. C.
I	9.477	140.13	14.8	160.52	15.1
II	7.911	220.04	27.8	212.94	20.1
III	9.021	134.49	14.9	150.70	14.2
IV	8.554	231.48	27.1	262.08	24.7
V	9.727	121.08	12.4	147.42	13.9
VI	8.407	247.55	29.4	262.08	24.7
VII	9.115	124.94	13.7	119.34	11.3
VIII	7.933	229.21	28.9	172.54	16.3
IX	9.219	118.98	12.9	117.00	11.0
X	8.883	244.67	27.5	180.18	17.0
XI	10.216	134.16	13.1	118.40	11.2
XII	8.261	216.53	26.2	180.18	17.0
XIII	9.829	122.96	12.5	124.02	11.7
XIV	9.046	244.47	27.0	193.28	18.2
XV	10.289	107.07	10.4	124.49	11.7
XVI	9.263	256.13	27.7	191.10	18.0

Geometrically calculated volume:	$M = 9.07 \pm 0.18$ c. cm., $\sigma = 0.73 \pm 0.13$ c. cm.
Geometrically calculated surface:	$M = 180.9 \pm 14.6$ sq. cm., $\sigma = 58.5 \pm 10.3$ c. cm.
Geometrically calculated mastication coefficient:	$M = 20.7 \pm 2.0$ sq. cm./c. cm., $\sigma = 8.0 \pm 1.1$ sq. cm./c. cm.
Real volume:	10.6 c. cm.
Colour-determined surface:	$M = 169.8 \pm 11.8$ sq. cm., $\sigma = 47.1 \pm 8.3$ c. cm.
Colour-determined mastication coefficient:	$M = 16.0 \pm 1.1$ sq. cm./c. cm., $\sigma = 4.4 \pm 0.78$ sq. cm./c. cm.

The difference between the geometrically determined surface and the colour-determined surface is  $11.1 \pm 18.8$ , therefore lying within the limits of the standard error. The difference for the mastication coefficients is  $4.7 \pm 2.3$ , so they agree satisfactorily. Nor are there any statistically significant differences as regards the variability. Now, the number of determinations is not great, and perhaps, in a larger material, it might be possible to show systematic deviations between the two methods of determining surface and mastication coefficient. All that is of interest to establish in this connection is, that any such deviation should be moderate in size, and that results are reached in the colour-determination of the surface that may be used to verify the values obtained by a geometrical calculation.

## Chapter 7.

### Summary: The standard method and its errors.

The standard method chosen as a result of the investigations made can be briefly characterized as follows.

For material, pieces of 15 per cent gelatin and 5 per cent barium sulphate have been used. The pieces were hardened for 24 hours in a solution consisting of 350 g. of water and 50 g. of 36—38 per cent formalin solution. The pieces had a volume of 10.6 c. cm. and a weight of 11.4 g. The material fulfils certain demands as regards compressibility and resistance. By this means it can be checked whether the material has the character required in the standard tests.

In the test, the subject is asked to chew the piece either until he considers it ready to swallow, or else for a certain number of times. When carrying out the test, different procedures have been used as regards this; they will be discussed later. The test subject then spits out the piece into a glass, and it is divided up into fractions by means of water-straining in a special apparatus. For this are used a pressure of 100 cm. of water, a reversing of the flow with an interval of 12 seconds and a straining time of 48 seconds during 6 minutes. After this, the particles in the 7 coarser fractions are counted, and the volume of those in the 3 finest fractions, where the strainer holes were 3, 2 and 1 mm. in diameter, is determined in graduated glass tubes by sedimentation in water. In estimating the degree of reduction, special formulas have been used to calculate the portion's total volume, its total surface, and, finally, the mastication coefficient giving surface per volume unit. Already in the preliminary experiments, distinct differences could be established between the results when the subjects had gone on chewing as long as they wished and when they had only chewed 40 times, as also differences in chewing by people with good and bad sets of teeth

respectively. The more effective the chewing, the greater the portion's surface per volume unit. These problems will be discussed in Part II.

The standard error of the method has been calculated with the help of double determinations (cf. Table 7). It has been found that the error of measurement attached to a single determination of a mastication coefficient, and which is conditioned by errors in the actual straining, is about 2.1 per cent (cf. Table 7). The standard error obtained for a determination of a mastication coefficient when a given person chews repeatedly, is much greater, due to the fact that a subject does not chew in exactly the same way when he performs a test more than once. This error seems to be greater for men, 10.3 per cent. than for women, 8.6 per cent. (Cf. Tables 49 and 60.) It is, of course, not possible to escape this variability by improving the methods. If the mastication coefficient is determined for someone with a single test, there are, all the same, not inconsiderable factors of uncertainty to reckon with, and if a more reliable orientation of a person's mastication is wanted, he must be subjected to a series of tests.

Considering that the error in the determination of the mastication coefficient by straining is comparatively small, this method is, as a matter of fact, fairly exact. Further, it does not take much time, so that it is well suited for mass investigations. It also seems reasonable to assume that the method could be used for practical tests of judging the masticatory powers in separate patients; though in individual cases like that, a series of tests should be made, in order to reach reliable mean values. If, for instance, 10 tests are made on an individual, the standard error of the mean of the tests should be about 3 per cent.

## Part II.

# Investigation of mastication with complete and with more or less defective sets of teeth in men and women of different ages.

### Chapter 8.

#### Introduction.

In the previous section we have stressed the desirability of getting an idea of the mastication effect and its relation to the number of the teeth. The method worked out and described here is sufficiently exact and, at the same time, does not take so long as to render it impossible to investigate a material large enough to provide a survey of how effectively persons chew in an average population.

When selecting material for investigation, certain viewpoints ought to be taken into consideration. We must reckon with the possibility of there being differences in the mastication effect both between men and women with similar sets of teeth, and also for different ages. From these points of view, it is advisable to investigate the same number of men as women, as far as this is possible, and also to keep material concerning children, adults and old people all separate from one another in the experiments. Then, a most important consideration, people with more or less complete sets of teeth may be expected to chew with different effectivity. The investigation material should therefore be grouped with regard to the quality of the sets of teeth. It is of special interest, finally, to investigate how people with complete dentures chew, and, in so doing, also compare the masticatory powers here with those in people with their own teeth.

Using as basis the investigation material comprising the different groups indicated here, it should be possible to reach a fairly well differentiated picture of some of the physiological features involved, and get something to go on for an estimation of the masticatory powers under different conditions, specially in a defective set of teeth and an artificial denture; all this may well yield information which is also of some value for practical dentistry.

## Chapter 9.

### Material.

The material for investigation has been mainly collected in schools, regiments, factories and almshouses. Guided by the viewpoints given above, the subjects were divided into the following groups.

I. *Children.* The group consisted of schoolchildren, half with their milk teeth and half with permanent sets. There were 50 boys and 50 girls of 7 years of age, and 50 girls and 50 boys of 13 years of age.

II. *Adults with their own teeth.* The investigated persons were conscripts and older mobilized classes, and women of corresponding ages — i. e. 20 — 45 years. 62 persons over 35, but not over 45, were included in this group, but only such whose sets of teeth were not considered to show age changes. There were 229 men and 237 women.

III. *Older persons with their own teeth.* The investigated persons were from 50—75 years of age. There were 101 men and 50 women. The men were examined at a workhouse in Stockholm; neither in factories nor almshouses was it possible to find more than a very small number of women with their own teeth who were suitable for investigation. The material consisted mainly of persons who volunteered for investigation in my clinic.

IV. *Adult and older persons with full dentures.* The investigated persons were about 40—80 years of age, and consisted of 50 men and 50 women.

When judging whether a set of teeth is 'good' or 'bad' from a functional point of view, it is necessary in some way to evaluate the teeth that are antagonists and that can function completely.

A number of authors have discussed evaluation questions of this kind.

One of the first who attempted to submit figures for the mastication value of the teeth was FEILER (1916). He reckoned a functioning molar as one unit, and a bicuspid as half a unit. He ascribed no mastication value to incisors and canines. Different scales of values have later been drawn up by a number of authors. MICHAELIS (1920) reviews the literature in this field without, however, advancing any suggestion of his own. HENTZE (1917) uses, for example, the following scale: incisors and canines are each one mastication unit; the first bicuspid is 2 units; the second bicuspid 3 units; the first and second molars each 6 units. The third molar is not thought to have any value. ROHRER (1919) uses the following scale: incisors and canines each 0.25 mastication units; bicuspids and the first and second molars each one unit; the third molar 0.5 of a unit.

These scales are only given here as examples. They are *a priori* estimates and are not based on empirical investigations. Nor do they take into consideration that teeth do not consistently correspond to one another: a grinder in the lower jaw has for instance occlusion with parts of several teeth in the upper jaw.

In this paper the author has first of all registered the number of teeth. This number does not, of course, give any definite conception of the effectivity of the set; this can be estimated with more certainty by the number of occlusion contacts between the two rows. It is all the same impossible to determine the contacts exactly without first making models of jaws and teeth and mounting these in an articulator. In a mass investigation, it is necessary to classify the sets of teeth quickly, and at the same time with reasonable certainty. In doing this, the author used an *a priori* enumeration of points, according to which the surfaces of the teeth are imagined as divided into sections. In an inspection of the rows of teeth in central occlusion, we can tell which sections in the upper and lower jaws correspond to one another. A contact between two sections is given 1 point. Figure 5 shows how the calculation of points for an ideal set of teeth is carried out.

It is seen from the schematic figure that molars, with the exception of the wisdom teeth in the upper jaw, are divided into three sections; further, that pre-molars and canines are divided into two sections. The other teeth are not divided.

A classification of the set of teeth from a *functional* point of view can now be made by counting the number of points for

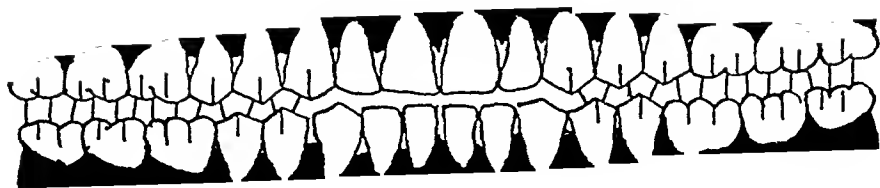


Fig. 5. Points of contact for the grinders in a normal set of teeth.

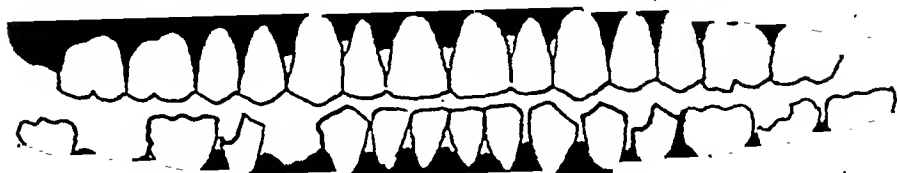


Fig. 6. A defective set of teeth with regard to calculation of points of contact. Compare Fig. 5 and the text.

grinders, canines and incisors. The canines assume an intermediate position inasmuch as the distal section of these teeth is reckoned as a grinder and the mesial section as an incisor. The value of the points should give a fairly good picture of the variation, set up not only by losses in teeth but also by anomalies in occlusion and position, in the number of contacts. A complete set of teeth has 32 contacts, 26 to the grinders and 6 to the incisors.

It has also been of interest to determine with a point scale the extent to which the sets of teeth investigated were defective as regards missing teeth and loss of substance in those that were left — in other words, to classify the sets from an *anatomical* point of view, independent of how far contacts may be present for such teeth as remained. Intact teeth — i. e. teeth with no loss of substance — were given 1 point. Defective teeth had 0.75, 0.50 and 0.25 points, according to the extent of the substance lost. 0 signified root stumps and missing teeth.

Figure 6 shows how the calculation of points in a defective set of teeth has been made. The defective set of teeth in the figure



shows 14.50 points for molars and pre-molars (grinding teeth), and 12 points for canines and incisors (cutting teeth). The total for the whole set is 26.50 points.

With the help of a calculation of points of contact the sets can be classified as extremely good, good, bad and extremely bad. As the investigation is intended to work out the effect of mastication, the sets have been grouped with regard to the number of contacts for the grinders. The limits used have been chosen to lie between 26—16 points for extremely good sets, 15—11 for good sets, 10—8 for bad sets and 7—0 for extremely bad sets.

It has already been said that the calculation used is entirely arbitrary. A more rational procedure is to determine the area of the *occlusion surface*. To this end, each test subject with his own teeth was made to bite into a wax plate, 2 mm. thick, care being taken to see that this was done in central occlusion. The wax impression is transferred onto a film, and its surface determined with a planimeter. The value obtained gives the surface in sq. mm. Completely misleading results can be obtained in isolated cases, on account of incorrect biting when the test was made. To get comparable values, the persons investigated were instructed to bite on the wax with the teeth in central occlusion. If this is done with the lower jaw in protrusive or in lateral occlusion, the surface of the wax impression will be smaller. If, on the other hand, the lower jaw then slips into central occlusion, the impression surface will be larger than it is after a direct bite in central occlusion.

The wax impression had a thin, transparent, inner zone with sharp borders, and an outer one which was thicker and had rather indistinct borders. When copying the impression, the outermost contours were followed, in order to get a maximal value for its surface.

Double tests have been made to get an idea of the method's sources of error, and its standard error has been calculated from the differences. The error of measurement is due partly to the biting in two separate tests not being exactly alike, partly, too, to the fact that the transference of the wax impression to a film, and the measuring of one and the same specimen, do not give exactly the same values in two copyings and measurings. The total error, which consequently consists of errors in biting and in technique, has been determined on 25 persons and amounts

TABLE 13.

Distribution of the material with regard to age and sex.

Age, years	Men	Women	Old men	Old Women	Full prosthesis		Total		Both sexes
					Men	Women	Men	Women	
7	50	50					50	50	100
13	50	50					50	50	100
16—19	13	20					13	20	33
20—24	146	65					146	65	211
25—29	25	58					25	58	83
30—34	26	48				2	26	50	76
35—39	9	33			1		10	33	43
40—44	8	12			1		9	12	21
45—49	1	1	1	5	3	1	5	7	12
50—54	1		15	19	7	2	23	21	44
55—59			19	13	10	2	29	15	44
60—64			35	6	11	4	46	10	56
65—69			20	3	12	6	32	9	41
70—74			10	2	4	9	14	11	25
75—83			1	2	1	24	2	26	28
Total	329	337	101	50	50	50	480	437	917

to 2.7 per cent in a single determination. For a further idea of the technical error, 25 wax impressions have been copied twice and their surfaces determined twice, the standard errors being calculated from the differences. The error which attaches to one diagram and measuring amounts to 1.7 per cent. It is thus found that the total standard error of 2.7 per cent is composed of a »biting» error of 1.7 per cent and a »technical» error of 1.7 per cent. It may be said that the actual measuring can be carried out fairly exactly. The most important source of the technical error lies in the copying, which was to be expected. Of course it is to be expected that systematic errors also play a part. However, it is not necessary to discuss them in this connection, as all the determinations have been made in the same way by one and the same person.

In the following pages, it has been investigated how far the calculation of points according to the author's scale has given values that run parallel with those obtained in the determination of surface. The determination of surface has, furthermore, been used throughout the treatment for an analysis of the masticatory effectivity, as this latter has been considered more reli-

able under all circumstances. As the investigation shows, however, a satisfactory measurement of the occlusal surface can be got from the point scale, too, so that this can be used if time does not allow the more laborious determination of the occlusion surface.

Table 13 collocates the investigation material grouped with regard to age and sex. The table shows the total material to comprise 917 persons. The intention has been to get about 50 individuals in each group exemplifying different sets of teeth, and this was possible to do for adult men and women. As far as children were concerned, the author has been content with about 50 for each class of age, if boys and girls are put together. It has, however, not been possible to get so large a material for the group with extremely bad sets of teeth. When it comes to older men and older women, the author has had to put up with a smaller material, as also in question of persons with full dentures. The difficulties of getting further material have been great, and the extent of that in hand has been considered sufficient, with the background of the larger adult groups, to allow of a comparison. As regards individuals with full dentures, no more will be said here than that they have been classified in three groups: those with extremely good, good and bad sets of teeth respectively, and that this grouping has subjective judgments at the back of it. We shall be discussing these questions in more detail later in this paper.

## The taking of specimens.

Each investigated person was made to chew five test portions one after the other. Between each portion, he was made to rinse out his mouth three times, and the water with which this was done was kept. In cases with full dentures, these were also taken out and sluiced with water, which was afterwards saved. The number of chews each time were counted. This was not as a rule a difficult process, except in isolated cases when the test subject chewed with small and rapid movements of the jaws. The chewing movements were counted in 130 tests by two people simultaneously. The differences in the standard errors showed a difference of  $-1.26 \pm 0.41$ , bordering on statistical significance. The difference is so small as to have no importance, and would seem to show that such counts can be made with satisfactory exactitude.

The *first* test portion was chewed just as the test subject liked: he was not influenced in any way. The idea of this was to provide some practice for subsequent tests. The portion was all the same saved and analysed, as it was, of course, of interest to determine the results and number of the chews.

The *second* and *third* portions were chewed on the express instructions to chew until the mass felt ready to be swallowed in the same way as if it were food. It should be mentioned that there is a difference in the chewing here, compared with that of food: in the latter case, one swallows while chewing, so that the whole of the mouthful does not go down at once. To get a control, a third mastication test was made, consisting of a repetition of the second; this time, too, the subject was told to chew until he felt ready to swallow.

Over and above this free mastication, where the test subjects themselves determined the number of times they chewed, two tests were made where the test portion was *chewed 20 and 40 times*. By fixing the number of chews, it becomes possible to com-

pare the results without risking differences conditioned by variations in this respect.

Inspecting the teeth of the patient, entering the details and taking of the specimen require a total time of 20—30 minutes. The analysis of five specimens takes, on an average, an hour. Generally, a larger number of specimens was taken at one time, so that it was sometimes a day or so before they were analysed. For this reason it was considered advisable to conserve them by adding a few drops of formalin to each.



TABLE 14.

Theoretical (*T*) and observed (*N*) number of teeth in 229 grown-up men.

Type of teeth	Number of teeth		
	<i>T</i>	<i>N</i>	<i>N</i> in % of <i>T</i>
Total number of teeth.....	7328	5815.25	79.4
Cutting teeth .....	2748	2698.00	98.2
Grinding teeth, of which ....	4580	3117.25	68.1
Wisdom teeth .....	916	396.50	43.3
Other grinding teeth .....	3664	2720.75	74.3

between calculated, maximal and actual number. Incisors and canines were missing only in 1.3 per cent of the calculated number, grinders — with the exception of wisdom teeth — were present in three-quarters, i. e. missing in 25.7 per cent, and the wisdom teeth were missing or had not come through in more than half, i. e. 56.7 per cent.

It is not always easy to decide if a tooth is a wisdom tooth or not. The author had not the opportunity of taking x-ray pictures in dubious cases. Consequently, the figures given here and in the following must be taken with some reservation.

If the set of teeth is evaluated in respect of mastication efficiency according to number of teeth, we run the risk of passing erroneous judgments. The loss of an occluding grinder deprives the antagonist tooth wholly or partially of its function. As has been said before, when the teeth are in an antagonist position, the loss of one is equal to the loss of two. In order to get a more detailed registration of the set of teeth, the number of contacts between occluding pairs of teeth has therefore been calculated in a way already given, namely estimating the approximate area of those tooth surfaces that meet in central occlusion. A survey of maximal and observed number of occlusion contacts is given in Table 15.

As was expected, it is found that the number of actual contacts is far lower than the maximal number. The difference is less for incisors, for which the actual number is 83.6 per cent, than for grinders (with the exception of the wisdom teeth); for these, only half, or 51.1 per cent, of the calculated contacts are found. The wisdom teeth seem to show in not quite a quarter, or 23.2 per cent.

TABLE 15.

Theoretical ( $T$ ) and observed ( $N$ ) number of contacts of teeth in 229 grown-up men.

Type of teeth	Number of contacts of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth.....	7328	3808	52.0
Cutting teeth.....	1374	1149	83.6
Grinding teeth, of which ....	5954	2659	44.7
Wisdom teeth .....	1374	319	23.2
Other grinding teeth .....	4580	2340	51.1

Following the distribution of grinding teeth contacts in the material, it has been made into four groups with their limits at median and quartiles. A calculation shows that the lower quartile lies at 7.7 points, the median at 11.0 points, and the upper quartile at 15.9 points. According to this calculation, group I (extremely good sets of teeth) falls within the limits 26—16 points inclusive, group II (good sets of teeth) within the limits 15—11 points, group III (bad sets of teeth) within the limits 10—8 points, and group IV (extremely bad sets of teeth) within 7—0 points inclusive.

The limits are motivated by the actual distribution of the number of occlusion contacts among the individuals investigated. Theoretically, it would, of course, be possible to give other class limits; however, it has been considered necessary to let practical statistical viewpoints decide the grouping. The limits given make possible a statistical analysis of the material of a more satisfactory kind. In another material it may prove suitable to set other limits and to use more or fewer groups. The limits given now have, however, been used throughout the whole investigation, since comparison with the conditions in adult men is thereby rendered possible.

With regard to the grouping of the conscript material according to the number of occlusion contacts in the classes given above, it may be of interest to see how the average number of teeth is distributed within the different groups. (Cf. Table 16.)

The table shows that the average number of grinders gets fewer as the occlusion gets worse, while the number of incisors remains fairly constant. The difference in the average number of incisors in group I (extremely good sets of teeth) and group



TABLE 16.

Number of teeth in grown-up men, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth		$n$	$M \pm \epsilon(M)$	$\sigma$
Grinding teeth				
Group	I: extremely good	63	$17.83 \pm 0.18$	1.44
,	II: good	60	$15.13 \pm 0.19$	1.48
,	III: bad	51	$12.41 \pm 0.24$	1.71
,	IV: extremely bad	55	$8.82 \pm 0.38$	2.81
Cutting teeth				
Group	I: extremely good	63	$11.921 \pm 0.039$	0.311
,	II: good	60	$11.838 \pm 0.055$	0.423
,	III: bad	51	$11.676 \pm 0.073$	0.524
,	IV: extremely bad	55	$11.659 \pm 0.123$	0.911

IV (extremely bad sets of teeth) is not statistically significant (difference  $0.26 \pm 0.13$ ). It ought to be expected that if the grinders are extensively defective, then the incisors, too, would be in less good condition. A calculation of the difference in standard deviation between incisors in extremely good and in extremely bad sets of teeth also shows that the difference is statistically significant ( $0.600 \pm 0.001$ ). When the grinders are poor, the incisors display an increased variability, indicating that they, too, are not so good in a number of cases, although the average number of incisors shows no significant difference between the groups.

Table 17 gives an idea of how far the average number of occlusion contacts agrees with the theoretical class midpoint in the different groups. The figures in the table show that the average number of occlusion contacts for group I (extremely good sets of teeth) is somewhat lower than the theoretical centre. The average number in the middle groups II and III (good and bad sets of teeth) agree well, on the other hand, while the average number for group IV (extremely bad sets of teeth) is rather higher than the theoretical centre.

The above grouping into four, with limits set by median and quartiles, gives groups with class ranges comprising different

TABLE 17.

Number of contacts of teeth in grown-up men, divided into groups with sets of teeth in varying condition. The class limits are: for group I, 26—16 mastication contacts, for group II, 15—11 mastication contacts, for group III, 10—8 mastication contacts, for group IV, 7—0 mastication contacts. Theoretical class midpoint =  $T$ .  $n$  = number of persons.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$T$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth				
Group I: extremely good	63	21	$18.54 \pm 0.32$	2.51
» II: good	60	13	$12.57 \pm 0.17$	1.32
» III: bad	51	9	$9.12 \pm 0.12$	0.86
» IV: extremely bad	55	3.5	$4.95 \pm 0.25$	1.82
Cutting teeth				
Group I: extremely good	63	—	$5.35 \pm 0.16$	1.29
» II: good	60	—	$4.93 \pm 0.21$	1.60
» III: bad	51	—	$4.90 \pm 0.22$	1.55
» IV: extremely bad	55	—	$4.84 \pm 0.25$	1.85

numbers of occlusion contacts. Thus, 11 points correspond to group I, 5 points to group II, 3 points to group III and 7 points to group IV. A smaller number of points in the middle groups compared with the extreme groups should mean a greater variability in these latter. It is therefore not necessarily the case that, in reality, there is a sufficient number of sets of teeth with point totals tending towards the highest class limit in group I, and the lowest in group IV, to give a noticeable increase in the variability.

The figures in the table show, as a matter of fact, that the values for standard deviation and variation coefficient display shifts in these directions. The difference in the variability between the extreme groups is not statistically significant. On the other hand, that between the standard deviations for group I and group III is significant (difference  $1.65 \pm 0.21$ ), as is also the one between group I and group II (difference  $1.19 \pm 0.25$ ). We shall be discussing this problem again when investigating the mastication coefficient for these groups.

When evaluating the set of teeth with regard to the masticatory effectivity, the author has, for reasons previously given, proceeded on the belief that the number of occlusion contacts

gives a safer foundation for the estimation than the number of teeth. It has been seen that we get lower figures for the number of occlusal contacts compared with the number of grinding teeth. By comparing the figures in Table 16 with corresponding figures in Table 17, it is possible to get an idea of the relation borne by the average number of grinders in the different groups I—IV to the average number of contacts. The tables give figures for the number of grinders per occlusion unit; in extremely good sets of teeth, there are 0.93, in good sets of teeth 1.20, in bad sets of teeth 1.36 and in extremely bad sets of teeth 1.78. In a normal set of teeth, where none are missing, 0.80 of a tooth goes to each contact. The figure series shows that, as has already been pointed out, several teeth in a defective set have no functional significance. The calculated *contact coefficient* makes more exact comparisons possible, and the coefficient suggested here is to some extent suitable as a gauge of different sets of teeth.

The set of teeth can also be evaluated with regard to masticatory effectivity by measuring the impression of the two rows on a wax plate. In describing the method in Chapter 8, it was mentioned that misleading results might be obtained in isolated cases, both from incorrect biting on the wax and from the transference of the impression to a film and the measuring of the figures obtained in this way.

Obviously faulty specimens, due to biting wrong, have been discarded and taken afresh. As has been said before, a calculation has been made of the method's standard error in a single determination. This error is small (i. e. 2.7 %).

The estimation of the set of teeth according to the calculated number of occlusion contacts goes considerably quicker than the measurement of the occlusion surface area, and if this method proves sufficiently exact, it should perhaps be preferred, in certain cases, to the later one. Nevertheless, in the present investigation both methods have been used throughout.

Under all circumstances, however, information is needed as to how far the estimation of contacts and determination of surface agree. A calculation of the correlation between the number of occlusal contacts and the values of the occlusion surface area have been carried out on 226 conscripts and older mobilized classes. A correlation coefficient of  $r = 0.86 \pm 0.02$  was obtained. As regards the schematized estimation of a set of teeth accor-

TABLE 18.

Occlusion surface in sq. mm. of grinding teeth in grown-up men, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \varepsilon(M)$	$\sigma$
Group I: extremely good	63	$435.6 \pm 11.2$	89.0
> II: good	60	$326.8 \pm 8.4$	64.9
> III: bad	51	$250.0 \pm 8.1$	58.1
> IV: extremely bad	53 <sup>1</sup>	$155.3 \pm 8.9$	64.7
Total	227	$299.7 \pm 8.3$	125.7

ding to the number of contacts, in a small number of classes, it is surprising to find so good an agreement with the varying values obtained from the surface determinations. The high correlation shows that it is possible satisfactorily to classify the sets of teeth according to the number of occlusion contacts in the way described in Chapter 9.

Table 18 gives a survey of the average value of the occlusion surface area within the four groups, the grouping being done according to the number of occlusion contacts. The mean values in the table display good parallelism, in that equally large differences of about 100 sq. mm. are obtained between the groups. The figures show that the surface values exhibit a somewhat larger variability in per cent than the one found in evaluating the number of occlusion contacts for grinding teeth. This is probably due to the fact that the area of the occlusion surface varies in teeth with the same numeral. To facilitate the estimation of the number of contacts, the surfaces of the grinding teeth, as mentioned above, have been divided up into sections, two sections which meet on occlusion being given the value of a contact. It could not be taken into consideration here that the sections are, in some cases, on teeth with a comparatively large occlusal surface, and in other cases on teeth with a comparatively small one. It is therefore clear that we can expect a fairly large variability in the measured surfaces within the groups, since the grouping was done according to the number of contacts. Deviations of this sort counterbalance one another

<sup>1</sup> Information is lacking regarding 2 cases of 55.

TABLE 19.

Theoretical ( $T$ ) and observed ( $N$ ) number of teeth in 237 grown-up women.

Type of teeth	Number of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	7584	5887.50	77.6
Cutting teeth	2844	2804.00	98.6
Grinding teeth, of which	4740	3083.50	65.1
Wisdom teeth	948	266.75	28.1
Other grinding teeth	3792	2816.75	74.3

in such a way that the means run fairly parallel in both series of figures.

A comparison of the variability for the different groups yields differences of the same kind as in the investigation of the variation in the number of contacts. The difference between group I and group III is statistically significant (difference  $30.9 \pm 9.8$ ).

*Set of teeth in adult females.*

Of the investigated adults, somewhat more than half, or 237 persons, consisted of *female* factory-hands in Stockholm from 16—45 years of age. All investigated persons have been included, and the material is probably fairly representative of the population group in question. A survey of the number of teeth in adult females is given in Table 19.

The figures in the table show an extremely small difference between the calculated maximal number of incisors and their actual number. They are missing only in 1.1 per cent of the calculated number. Grinders, with the exception of wisdom teeth, are present to three fourths, or 74.3 per cent, and wisdom teeth to one fourth, or 28.1 per cent of the calculated maximal number. As is seen on comparison with the figures in Table 14, there is surprisingly good agreement in the number of their teeth between men and women of corresponding ages. The only difference is found in the number of wisdom teeth, which in women are only present in 28.1 per cent, to 43.3 per cent in men.

A registering of the sets of teeth according to the number of grinder occlusion contacts gives values which also agree re-

TABLE 20.

Theoretical ( $T$ ) and observed ( $N$ ) number of contacts of teeth in 237 grown-up women.

Type of teeth	Number of contacts of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	7584	3929	51.8
Cutting teeth	1422	1150	80.9
Grinding teeth, of which	6162	2779	45.1
Wisdom teeth	1422	260	18.3
Other grinding teeth	4740	2519	53.1

markably well with the corresponding values in men. A survey of the number of contacts for incisors and grinders is given in Table 20.

In adult women, as in adult men, we find far lower figures for the actual number of grinder contacts compared with the calculated one. Incisors, on the other hand, are found in 80.9 per cent of the calculated number. The number of grinder contacts (with the exception of the wisdom teeth) amounts to half, or 53.1 per cent, and the number of contacts for wisdom teeth to not quite a fifth, or 18.3 per cent, of the maximal calculated

TABLE 21.

Number of teeth in grown-up women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

$\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth			
Group I: extremely good	61	16.15 $\pm$ 0.16	1.21
" II: good	76	14.11 $\pm$ 0.16	1.41
" III: bad	50	12.15 $\pm$ 0.24	1.71
" IV: extremely bad	50	8.37 $\pm$ 0.28	2.00
Cutting teeth			
Group I: extremely good	61	12.00	0
" II: good	76	11.934 $\pm$ 0.033	0.286
" III: bad	50	11.835 $\pm$ 0.058	0.411
" IV: extremely bad	50	11.465 $\pm$ 0.138	0.977

TABLE 22.

Number of contacts of teeth in grown-up women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17. Theoretical class midpoint =  $T$ .  $n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth		$n$	$T$	$M \pm \epsilon(M)$	$\sigma$
Cutting teeth					
Group	I: extremely good	61	21	$17.87 \pm 0.22$	1.73
»	II: good	76	13	$12.87 \pm 0.15$	1.35
»	III: bad	50	9	$9.16 \pm 0.12$	0.83
»	IV: extremely bad	50	3.5	$5.06 \pm 0.23$	1.62
Grinding teeth					
Group	I: extremely good	61	—	$4.92 \pm 0.21$	1.60
»	II: good	76	—	$4.91 \pm 0.19$	1.63
»	III: bad	50	—	$4.78 \pm 0.28$	1.95
»	IV: extremely bad	50	—	$4.76 \pm 0.23$	1.66

number. A comparison with the figures in Table 15 shows that the difference in the number of contacts between men and women is very small. The agreement is, in other words, surprisingly good.

In order to work out the distribution of the material in more detail, median and quartiles have been calculated for grinder contacts. The calculation gives about the same values as for men, namely the lower quartile at 8.5 points, the median at 11.7 points, and the upper quartile at 15.7 points.

Table 21 gives a survey of the average number of teeth in the different groups of extremely good to extremely bad sets of teeth (groups I—IV). The division has been made according to the number of occlusion contacts within the limits which were given for adult men.

The figures show that the number of persons in the different groups agrees on the whole with the number we find among adult men. The comparison between adult men and women shows good agreement as regards the mean number of teeth, the standard deviation, and the variation coefficient (cf. Table 17).

Figures for the average number of occlusion contacts in groups I—IV are given in Table 22.

The figures in the table show that, with regard to grinding teeth, the average number of contacts gets smaller as the occlu-

sion gets worse, while the average number of contacts for incisors keeps fairly constant. The averages agree well with the values obtained for men (cf. Table 17). For adult women, too, the same differences in the values for the standard deviation are found as for adult men. The difference between group I and group III is statistically significant. (Difference  $0.90 \pm 0.18$ ). Other differences are not statistically significant.

It is possible to calculate the average number of grinders per occlusion unit from the values in Tables 21 and 22. For group I (extremely good sets of teeth) there are 0.90 grinders per occlusion unit, for group II (good sets of teeth) 1.09, for group III (bad sets of teeth) 1.32, and for group IV (extremely bad sets of teeth) 1.65. The figures agree well with the corresponding contact coefficients for adult men.

In the comparisons which have now been made between adult men and women of the same age, we thus find good accordance as regards both the number of teeth and the number of occlusion contacts. Taking into account the size of the materials compared, the possibility that a still larger material might reveal certain differences, in spite of the accordancess, cannot be excluded. As, however, the accordance can be termed very good, and as the materials are not unduly small, there is hardly cause to expect very great differences. It has further been ascertained that the classification of the sets of teeth which was worked out from the state of affairs in 229 adult men, can be used for women of corresponding ages, in that medians and quartiles roughly coincide, so that the number of persons in the groups will be about the same.

It now remains to compare the average occlusion surface for adult women with the means obtained when investigating men of corresponding ages. A survey of such mean values in groups delimited according to the number of occlusion contacts, is found in Table 23.

As expected, we find throughout lower means for women than for men (cf. Table 18). The difference between the means is  $26.3 \pm 14.1$  sq. mm. for group I (extremely good sets of teeth),  $4.7 \pm 12.1$  sq. mm. for group II (good sets of teeth),  $7.5 \pm 11.1$  sq. mm. for group III (bad sets of teeth), and  $11.3 \pm 12.2$  sq. mm. for group IV (extremely bad sets of teeth). The differences are small and not statistically significant; in so far as there are any, they no doubt indicate that the teeth of an adult woman



TABLE 23.

Occlusion surface of the grinding teeth in sq. mm. in grown-up women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \epsilon(M)$	$\sigma$
Group I: extremely good	61	$409.3 \pm 8.6$	67.0
" II: good	76	$322.1 \pm 9.1$	79.4
" III: bad	50	$242.5 \pm 7.6$	53.5
" IV: extremely bad	44 <sup>1</sup>	$144.0 \pm 8.4$	56.0
Total	231	$295.1 \pm 7.3$	111.5

are smaller than those of an adult man. That the difference is greater for group I may possibly be due to the fact that the number of occlusion contacts for wisdom teeth is lower in women than in men. This fact is very marked in the values in group I (extremely good sets of teeth), while in the remaining groups, on the other hand, wisdom teeth are probably missing to a large extent in both sexes. (It should be remembered that we find wisdom teeth in men in 43.3 per cent of the calculated maximal number, and in women in 28.1 per cent.)

If we compare the four groups in the female material with one another, we find equal differences of about 90 sq. mm. between the means. In a comparison of the variability between men and women, we find somewhat lower values in the latter, but not statistically significant differences.

#### *Set of teeth in old men.*

With increasing age the number of teeth deteriorates on account of losses, defects and the like. The degree of deterioration is connected not only with age but also with dental treatment received, and therefore with social standards, too. The *older men* in the material investigated were taken from Stockholm workhousers. The amount of dental care they had received was very slight, so that the results of the investigation give a picture of conditions in sets of teeth which on the whole have not been the subjects of therapeutic measures.

<sup>1</sup> Regarding 6 cases of 50, information is lacking.

TABLE 24.

Theoretical (*T*) and observed (*N*) number of teeth in 258 older men.

Type of teeth	Number of teeth		
	<i>T</i>	<i>N</i>	<i>N</i> in % of <i>T</i>
Total number of teeth	8256	3748.50	45.4
Cutting teeth	3096	2012.50	65.0
Grinding teeth, of which	5160	1736.50	33.6
Wisdom teeth	1032	214.00	20.7
Other grinding teeth	4128	1521.00	36.8

Table 24 gives a survey of the number of teeth in 258 men from 45—80 years of age. Of these, 15 were under 50, and 24 over 70.

As expected, figures are found which indicate a relatively poor number of teeth. Of the calculated maximal number, incisors and canines are present to about two thirds, grinders with the exception of wisdom teeth to about one third, and wisdom teeth to less than one fourth. A comparison between the number of teeth in adult and older men (cf. Table 14) shows that incisors are lacking in the latter in 35 per cent of the calculated number, and in the former in 1.8 per cent. Grinding teeth are lacking in older men in 63.2 per cent and in younger men in 25.7 per cent. Wisdom teeth are missing in older men in 79.3 per cent of the calculated maximal number, compared with 56.7 per cent in adult men. It is noteworthy that the difference is so large for grinders, but considerably less for wisdoms. It has been assumed that wisdom teeth decay very soon after eruption, on account of inferior calcification. The comparison of the number of wisdom teeth in younger and older men suggests that, to a large extent (in half of the cases where such were found), they decay early, but that in an appreciable number of cases these teeth survive an early caries and have comparatively good powers of resistance, so that they are kept right up to a ripe old age. Because of the diagnostic difficulties previously mentioned, this conclusion must be taken with some reservation.

Of the 258 people submitted in Table 24, 101 of them from 50—75 years of age have been tested with regard to powers of mastication. The number of teeth in these persons was better, since they were selected. Under such circumstances, it is hardly

TABLE 25.

Number of contacts of teeth in older men, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17. Theoretical class midpoint =  $T$ .  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$T$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth				
Group I: extremely good	15	21	$18.80 \pm 0.66$	2.54
» II: good	24	13	$12.71 \pm 0.24$	1.20
» III: bad	19	9	$8.89 \pm 0.19$	0.81
» IV: extremely bad	43	3.5	$4.23 \pm 0.33$	2.17
Cutting teeth				
Group I: extremely good	15	—	$5.73 \pm 0.21$	0.80
» II: good	24	—	$4.92 \pm 0.28$	1.35
» III: bad	19	—	$5.05 \pm 0.31$	1.35
» IV: extremely bad	43	—	$4.33 \pm 0.21$	1.36

of interest to give a detailed account of the nature of the teeth. In the grouping the same limits were used as for adult men.

A survey of the average number of occlusion contacts in the four groups is given in Table 25. The average number of occlusion contacts within the groups shows good agreement with the theoretical centre of the class for groups II and III. The groups I and IV show minor deviations, on the other hand.

The average number of grinders per occlusion unit gives, as is to be expected, rising figures: for group I, 0.83 teeth, for group II, 1.60 teeth, for group III, 1.25 teeth and for group IV 1.65 teeth.

The occlusion surface has also been determined for the older men. As Table 26 shows, 20 values are missing in group IV. The reason for this is that specimens taken from persons with few contacts were discarded, because the wax impressions were not so suitable for determining surface.

The values for the average occlusion surface are throughout higher than the values we found in adult men (cf. Table 18). The difference between adult men and older men is for group I (extremely good sets of teeth)  $96.4 \pm 27.0$  sq. mm., for group II (good sets of teeth)  $59.9 \pm 19.4$  sq. mm., for group III (bad sets of teeth)  $44.7 \pm 22.4$  sq. mm., and for group IV (extremely bad

TABLE 26.

Occlusion surface of the grinding teeth in sq. mm. in older men, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \varepsilon(M)$	$\sigma$
Group I: extremely good	15	$532.0 \pm 24.6$	95.1
"  II: good	24	$386.7 \pm 17.5$	85.8
"  III: bad	19	$294.7 \pm 20.9$	91.2
"  IV: extremely bad	23 <sup>1</sup>	$198.7 \pm 12.7$	60.9
Total	81	$338.6 \pm 15.8$	141.9

sets of teeth)  $43.1 \pm 15.5$  sq. mm. The differences for groups I and II are statistically significant; that for group III, on the other hand, is not. In group IV the difference is statistically probable. The difference between adult and older men in extremely good and good sets of teeth is probably due to the fact that the grinders in the older men investigated were abraded to a greater extent. A tooth with the cusps worn down gives a larger wax impression than an intact tooth, but this does not mean that the smooth occlusal surface need necessarily be larger in actuality than the intact occlusal surface with high cusps. No difference in abrasion was found between groups III and IV, and no statistically significant difference in value between the occlusion surfaces was obtained.

If we finally investigate the variation, we find distinct differences as regards the number of contacts, so that the variability is larger in the extreme groups than in the middle groups. (Cf. Table 25). The difference between group I and group III is statistically significant (difference  $1.73 \pm 0.48$ ).

If we look at the variability for the occlusion surface on the other hand, we do not get corresponding differences, and the differences are nowhere statistically significant. Here, then, there is a remarkable lack of parallelism between the number of occlusion contacts and the occlusal surface measured in sq. mm. The lack of agreement may possibly be supposed to be connected with the abrasion of teeth in the old, which constitutes yet another reason for variation.

<sup>1</sup> Regarding 20 cases of 43, information is lacking.

TABLE 27.

Theoretical ( $T$ ) and observed ( $N$ ) number of teeth in 45 older women.

Type of teeth	Number of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	1430	237.50	16.6
Cutting teeth	530	190.50	35.9
Grinding teeth, of which	900	47.00	5.2
Wisdom teeth	180	0	0
Other grinding teeth	720	47.00	6.5

*Set of teeth in old women.*

In giving an account of the investigation material in Chapter 8, it was said that it was not easy to find *older women* with their own teeth in almshouses. The author has been for material through two almshouses, together housing 620 women from 60—90 years of age, and among these has only been able to find a few with their own teeth. It is noteworthy that the number of teeth is considerably worse among older women than in the group of older men (cf. Table 24). It must, however, be said that the materials are not wholly comparable. The male material has been taken from a workhouse and does not include particularly ancient individuals, as men who are sickly and quite unable to work on account of age are transferred to almshouses. It may therefore well be that if a material of men, corresponding with that of the women as regards age, were investigated, an equally bad result would be obtained. In any case, less differences could certainly be expected than those expressed here by the figures. As it was, most of the older women had dentures. A small number had no teeth at all, and only 45 had any of their own left. An occasional tooth could sometimes be found in those with dentures, however, especially in the lower jaw as a support for the false ones. A survey of the nature of the teeth in the 45 women who had their own teeth is given in Table 27.

The table shows that the women investigated had few teeth, with large differences between the calculated maximal and the actual number. Of the total calculated number, only one sixth, or 16.6 per cent, were found in reality. There were no wisdom teeth at all, and only 6.5 per cent of the calculated maximal number of other grinders. As the figures show, the number of teeth

TABLE 28.

Number of contacts of teeth in older women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17. Theoretical class midpoint =  $T$ .  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$T$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth				
Group I: extremely good	10	21	$18.90 \pm 0.46$	1.45
» II: good	17	13	$12.18 \pm 0.27$	1.13
» III: bad	12	9	$8.67 \pm 0.19$	0.65
» IV: extremely bad	11	3.5	$4.55 \pm 0.53$	1.75
Cutting teeth				
Group I: extremely good	10	—	$4.90 \pm 0.48$	1.52
» II: good	17	—	$5.71 \pm 0.11$	0.47
» III: bad	12	—	$5.25 \pm 0.46$	1.60
» IV: extremely bad	11	—	$5.18 \pm 0.33$	1.08

in these women was such as to compel their being referred to group IV, i. e. extremely bad sets of teeth. It was further found that the grinder occlusion contacts were missing or else so few that the material did not lend itself to an investigation of the mastication effectivity. Only a few individuals could be used.

The investigation material had therefore to be sought elsewhere. At factories and other places of work, there proved to be great difficulties in getting older women with their own teeth for an investigation. The material that has been tested with regard to masticatory powers is mainly taken from the author's private practice.

The older women investigated belonged, as a rule, to the more well-to-do classes, and consisted of persons who had looked after their teeth. The number of teeth was comparatively good, and displayed small differences compared with the number in adult women, in spite of the difference in the average age between the two materials. Incisors were found to practically the whole of the calculated number, being absent in 3.1 per cent, grinders except for wisdom teeth to about three fourths or 72.5 per cent and wisdom teeth to about one fourth or 22.9 per cent.

The material is divided into four groups within the same limits for the point values as were used for adult men. A survey of

TABLE 29.

Occlusion surface in sq. mm. in older women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.

$n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.

$\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \epsilon(M)$	$\sigma$
Group I: extremely good	10	449.0 $\pm$ 20.7	65.3
" II: good	17	308.2 $\pm$ 13.0	53.8
" III: bad	12	200.8 $\pm$ 13.5	46.6
" IV: extremely bad	10 <sup>1</sup>	132.5 $\pm$ 13.1	41.4
Total	49	274.6 $\pm$ 17.4	121.9

the average number of occlusion contacts within the four groups is given in Table 28.

In a comparison between the average number of occlusion contacts in adult and older women, we find them agreeing fairly well. In groups III and IV we have lower values for grinders and higher values for incisors. This contrast may possibly be explained by saying that, within certain limits, there is a connection between the lower number of grinder contacts and the higher number of incisor contacts, which means a decrease in the set of teeth and thereby a slight increase of the incisor contacts. This holds good of older men, too. This assumption is backed up by the fact that differences as concerns both grinders and incisors are only found in groups III and IV, i. e. in bad sets of teeth. The average number of grinders per occlusion unit shows 0.88 teeth for group I, 1.15 for group II, 1.21 for group III, and 1.79 for group IV.

The older women have not shown the same wear of the occlusal surface cusps as was found in the older men. Probably, therefore, we cannot expect such very great differences in the values for the occlusion surface area in a comparison of those in older women with corresponding values in adult women. A survey of the average values of the occlusion surface area in groups divided according to the number of grinder contacts, is given in Table 29.

The figures in the table show, when compared with the corresponding values for adult women in Table 23, that the average

<sup>1</sup> Regarding 1 case of 11, information is lacking.

TABLE 30.

Theoretical ( $T$ ) and observed ( $N$ ) number of teeth in 100 boys and girls at 13 years of age.

Type of teeth	Number of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	2800	2633.75	94.1
Cutting >	1200	1175.25	97.9
Grinding >	1600	1458.50	91.2

occlusion surface area in group I (extremely good sets of teeth) is larger, while in the other groups it is smaller. As the material is small and the differences not statistically significant, it is not possible to see whether there is any real difference in the area of the occlusal surfaces between adult and older women. It may be remembered that the average number of occlusion contacts is lower in older women just in groups III and IV; this should, in respect of the high correlation between occlusion surfaces and grinder contacts, give lower means for the occlusion surface in these latter groups.

#### *Set of teeth in children.*

In *children*, we have to reckon, as regards the number of teeth, with not altogether similar conditions for the sets as in adults, and this in certain respects prevents comparisons being made between the two. As is seen from the account of the investigation material in Chapter 8, some of the children investigated and tested for masticatory powers had permanent teeth, and some had their milk teeth. The material consists of schoolchildren from Stockholm, and can probably be regarded as representative in so far as all who came for investigation were included.

Table 30 gives a survey of the number of teeth in 100 *13-year-old children*, of which exactly half were boys and half girls. Taking into consideration the size of the material, it was not thought that a special differentiation of boys and girls would prove of interest.

The figures in the table show us that the difference between the actual number of teeth and the calculated maximal number is very small. Practically the whole of the total number is



TABLE 31.

Theoretical ( $T$ ) and observed ( $N$ ) number of contacts of teeth in 100 boys and girls at 13 years of age.

Type of teeth	Number of contacts of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	2600	1988	76.5
Cutting :	600	455	75.8
Grinding :	2000	1533	76.7

there, with the exception of incisors in 2.1 per cent and grinders in 8.8 per cent of the possible number, which in children of 13 amounts to 28. (44 children had 28 teeth.) Comparisons can now be made with the adults' teeth, as the wisdom teeth in tables for adults are kept separate from the other grinders. A comparison between 13-year-olds and adult men shows that the children investigated have a larger number of grinders. The difference is 16.9 per cent. On the other hand, the number of incisors in 13-year-old children is lower, with a difference of 0.7 per cent. This difference is small and may be due to chance.

The fact that most of the sets of teeth were complete has meant that the number of grinder occlusion contacts was very high, gaps in the rows being relatively rare. A survey of the actual and the calculated number of contacts is given in Table 31.

The figures in the table show the actual number of occlusion contacts for incisors to be missing in 24.2 per cent, and for grinders to be present to about three fourths — i. e. absent in 23.3 per cent — of the possible number. Contacts for adult men are missing in 48.9 per cent, and in 46.9 per cent for women. We find, in other words, about half of the grinder contacts in adult men and women, while in children there are about three fourths of the calculated number.

As the number of teeth among the 13-year-olds was largely good, the limits used in the material for grouping the sets into four could not be applied directly. A classification has been made following the distribution of grinder occlusion contacts in the material, with limits set at median and quartiles. The calculation shows that the lower quartile lies at 12.5 points, the median at 15.9 points, and the upper quartile at 18.1 points. According to this calculation, group I A (perfect teeth) falls within the

TABLE 32.

Number of contacts of teeth in thirteen-year-old children, divided into groups with sets of teeth in varying condition. The class limits are: for group I a, 20—19 mastication contacts, for group I b, 18—16 mastication contacts, for group II, 15—11 mastication contacts, for group III, 10—0 mastication contacts.

Set of teeth		<i>n</i>	<i>T</i>	$M \pm \epsilon(M)$	$\sigma$
Grinding teeth					
Group	Ia: perfect	18	19.5	$19.67 \pm 0.11$	0.49
»	Ib: very good	36	17	$17.08 \pm 0.14$	0.84
»	Ia + Ib: extremely good	54	.	$17.94 \pm 0.20$	1.42
»	II: good	37	13	$12.84 \pm 0.24$	1.44
»	III: bad	9	5	9.89	.
Cutting teeth					
Group	Ia: perfect	18	—	$4.78 \pm 0.50$	2.10
»	Ib: very good	36	—	$4.56 \pm 0.43$	2.56
»	Ia + Ib: extremely good	54	—	$4.63 \pm 0.32$	2.38
»	II: good	37	—	$4.59 \pm 0.29$	1.79
»	III: bad	9	—	3.89	.

limits from 20—19 points inclusive, group I B (very good teeth) within the limits 18—16 points, group II (good teeth) within the limits 15—11 points, and group III (bad teeth) within the limits 10—0 points. For group II (good teeth), the same limits could be retained as used previously, i. e. the limits from 15—11 points. Group I (extremely good teeth) has been divided up into group I A (perfect teeth) and group I B (very good teeth), and group IV (extremely bad teeth) has been added to group III (bad teeth) to form one group.

In consideration of the very good number of teeth in the 13-year-old children investigated, relatively high values for the average number of occlusion contacts can be expected. Figures are given in Table 32.

In a comparison with corresponding averages for adult men and women, we find good agreement for the groups designated in the tables as extremely good, good and bad — i. e. groups I A and I B together, groups II and III. The adult group styled extremely bad teeth is not found among the older children investigated.

A calculation of the number of grinders per occlusion unit

TABLE 33.

Occlusion surface in sq. mm. in thirteen-year-old boys and girls, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 32.  $n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \epsilon(M)$	$\sigma$
Group I a: perfect	18	$427.8 \pm 10.5$	44.4
» I b: very good	36	$396.4 \pm 9.0$	54.3
» II: good	35 <sup>1</sup>	$311.4 \pm 8.7$	51.3
» III: bad	9	267.8	
Total	98	$360.0 \pm 7.6$	74.9

for the different groups showed that practically all the teeth in group I had functional importance, and that, furthermore, only a relatively small number within groups II and III had no function at all. For group I A, the number of teeth per occlusion unit was 0.81, for group I B, 0.91, for group II, 1.05 and for group III, 1.17.

The investigated children had received dental treatment at school, and this no doubt contributed to their having a good number of teeth. The permanent teeth had as a rule come through completely, and many of the children still had the 6-year tooth. There is therefore reason to expect comparatively high values for the occlusion surface. A survey of the average occlusion surface for the four groups is given in Table 33.

The figures in the table show that the average value for the occlusion surface is high. The older children are found, in spite of the lack of wisdom teeth, to have biting surfaces which agree fairly well with the values displayed in adult men and women.

The youngest investigated children, i. e. 100 7-year-old boys and girls, had as a rule cut their 6-year tooth. The maximal number of teeth that a child can have at this age is 24, i. e. 20 milk teeth and 4 permanent teeth. A survey of the calculated and actual number of teeth is given in Table 34. The milk teeth and permanent teeth have not been kept separate here.

The figures in the table show that incisors are missing in 14.9 per cent of the calculated maximal number. The percentage figure is high, which is of course due to the fact that it is just

<sup>1</sup> Regarding 2 cases of 37, information is lacking.

TABLE 34.

Theoretical ( $T$ ) and observed ( $N$ ) number of teeth in 100 boys and girls at 7 years of age.

Type of teeth	Number of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	2400	1878.00	78.3
Cutting »	1200	1021.75	85.1
Grinding »	1200	856.25	71.4

at this age the child loses his first front teeth. Grinders (milk teeth and permanent teeth) are present to about three fourths, i. e. missing in 28.6 per cent, of the calculated number.

A survey of the number of occlusion contacts is given in Table 35.

The figures show that the number of occlusion contacts for grinders is high in relation to the number of teeth involved. Thus, in a comparison of percentages for the number of teeth and number of occlusion contacts between 7-year-old children and adult men (cf. Table 15), we find 17 per cent more contacts in the former, corresponding in both groups to about the same number of teeth. The comparison shows that the sets of teeth in 7-year-olds have relatively few gaps.

To discover whether the same limits for grouping the sets of teeth as were used for adult persons are suitable here, the distribution of the material was investigated with calculation of median and quartiles. This showed the lower quartile to lie at 6.8 points, the median at 9.3 points, and the upper quartile at 12.0 points. The distribution differs from the one found in the material for adult men and women, where the lower quartile

TABLE 35.

Theoretical ( $T$ ) and observed ( $N$ ) number of contacts of teeth in 100 boys and girls at 7 years of age.

Type of teeth	Number of contacts of teeth		
	$T$	$N$	$N$ in % of $T$
Total number of teeth	2000	1348	67.4
Cutting »	600	394	65.7
Grinding »	1400	954	68.1

TABLE 36.

Number of contacts of teeth in seven-year-old children, divided into groups with sets of teeth in varying condition. The class limits are: for group I, 20—16 mastication contacts, for group II, 15—11 mastication contacts, for group III, 10—8 mastication contacts, for group IV, 7—0 mastication contacts. Theoretical class midpoint =  $T$ .  $n$  = number of persons.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$T$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth				
Group I: extremely good	8	18	16.00	.
" II: good	29	13	$12.38 \pm 0.22$	1.21
" III: bad	35	9	$8.89 \pm 0.14$	0.83
" IV: extremely bad	28	3.5	$5.57 \pm 0.21$	1.10
Cutting teeth				
Group I: extremely good	8	—	4.13	.
" II: good	29	—	$3.72 \pm 0.25$	1.33
" III: bad	35	—	$3.97 \pm 0.23$	1.33
" IV: extremely bad	28	—	$4.07 \pm 0.24$	1.27

lies at 7.7 points, the median at 11 points and the upper quartile at 15.9 points. The difference is nevertheless not so great that the same limits cannot be used in grouping the sets of teeth — namely, according to the number of occlusion contacts from 20—16 points for group I, 15—11 points for group II, 10—8 points for group III and 7—0 points for group IV.

We have now found a relatively high number of grinder occlusion contacts in proportion to the average number of the grinding teeth. It can be of interest to see how the average number of such contacts is distributed over the four groups, with reference to the grouping's having been done according to the same limits as were used for adults. A survey is given in Table 36.

The figures in the table show a surprising agreement in the average number of occlusion contacts for grinders in the four groups with corresponding figures for adult men and women (cf. Tables 17 and 22).

The occlusion surface has also been determined for the youngest children. A survey of the average surface is given in Table 37.

As expected, we find lower values compared with the corresponding ones for 13-year-olds. The difference for good sets of

TABLE 37.

Occlusion surface in sq. mm. in seven-year-old boys and girls, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 36.  $n$  = number of persons.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$M \pm \epsilon(M)$	$\sigma$
Group I: extremely good	8	306.3	.
» II: good	29	$263.1 \pm 7.5$	40.4
» III: bad	35	$199.7 \pm 4.8$	28.2
» IV: extremely bad	26 <sup>1</sup>	$144.0 \pm 5.7$	29.3
Total	98	$212.4 \pm 6.3$	62.5

teeth (group II) is  $48.3 \pm 1.15$  sq. mm., and is statistically significant. The total average difference is  $147.6 \pm 9.9$  sq. mm.

In a comparison of the average value of the occlusion surface through the *whole of the investigation material*, we find the following values: for 13-year-old children  $360.0 \pm 7.6$  sq. mm., (for older men, who, however, constitute a selected material,  $338.6 \pm 15.8$  sq. mm.), for adult men  $299.7 \pm 8.3$  sq. mm., for adult women  $295.1 \pm 7.3$  sq. mm., (for a selected material of older women  $274.8 \pm 17.4$  sq. mm.) and for 7-year-old children  $212.4 \pm 6.3$  sq. mm. We find the greatest difference between 13-year-old children and 7-year-old children. The total average value for the occlusion surface for adult men and women lies about halfway between the values for 13-year-olds and 7-year-olds. The older men and women investigated are not representative for the respective age groups, so that a comparison with their values is of no very great interest.

It was thought unnecessary to compare the results obtained by the author with those in other investigations which have been carried out into the nature of the teeth in the average population of Sweden. Such investigations have been made to get some information with regard to the occurrence of caries, but are not intended to throw light on the sets of teeth from a functional point of view. On the whole, the materials have not been submitted to any close statistical analysis, so that the figures obtained cannot be compared with those submitted here.

<sup>1</sup> Regarding 2 cases of 28, information is lacking.

## **The number of chews in persons of different age and sex, and with different sets of teeth.**

The number of times a mouthful is chewed before being swallowed depends first and foremost on its character, i. e. it is influenced by sensations deriving from the degree to which the mouthful is reduced. Different food substances are chewed for different lengths of time. Conscious acts of will probably do not play such a very large part in normal chewing, even if such factors may be thought to have some influence when it is a question of special tests. It can be assumed without further discussion that more or less constant habits are formed in chewing. One person may chew carelessly, i. e. only a few times, another may chew each mouthful a large number of times. There are, in principle, two ways in which these habits can be thought to be determined: food of a certain sort may be chewed until a certain degree of reduction is reached, or it may be chewed a certain number of times, with not so much attention paid to the result obtained.

If the degree of reduction is the deciding factor, we should expect great average differences between persons with good and bad sets of teeth. Those with bad sets ought, as a rule, to compensate the lowered effectivity due to loss of teeth by chewing longer, for a larger number of chews must be needed to reach a result comparable with that from good sets. We should find a certain variability for persons with the same sort of teeth, but this ought to be less than the one obtained in a population where the sets of teeth, too, vary. In so far as the question is one of habits, the variation in the number of chews when a given individual chews successive portions of one and the same type of food substance should be comparatively small.

If, on the other hand, the more or less fixed habits refer to the number of chews, this number should, once the habits have been formed, be fairly independent of the conditions in the sets

of teeth. Persons with poor sets should, on an average, chew the same number of times as those with good sets. We would further expect to find the variation in the number of chews for persons with the same sort of teeth to be about as large as the one in a population where the sets of teeth vary, also. Then, too, we expect a relatively small variation when one person chews successive mouthfuls of a selected substance.

It is, of course, possible that the way in which an individual chews is determined both by factors referring to the number of chews, and factors conditioned by sensations due to the mouthful's degree of reduction. These principles will be taken into account in the investigation in the following pages of the number of chews used in the mastication tests by persons of different ages, different sex, and with different sets of teeth. Before these problems are discussed, however, an account will be given of investigations, made to get an idea of the importance the character of the test material has for the number of chews, and also of investigations into how far the test corresponds to chewing under normal circumstances.

### *Chewing materials of different types.*

Now, when chewing food, the number of chews varies with the consistency of the food and the size of the mouthfuls. In the investigation of test material of different consistency, described in Chapter 3, a small number of conscripts were made to chew in succession approximately the same amount of gelatin, carrot, white of egg, synthetic rubber and indiarubber. The test subjects, half of which had good sets of teeth, and half bad, were allowed to chew the different portions for as long as they themselves wanted. Table 38 gives figures showing how test portions of different consistency are chewed.

The table shows that white of egg is on an average chewed a very small number of times, after which the test subjects consider it ready to swallow. Indiarubber, on the other hand, seems hard to chew, and takes a relatively long time, though as the number of tests is small, the differences compared with other materials (with the exception of white of egg) are not statistically significant. When the sets of teeth are bad, we find no differences of any great importance between the other substances, i. e. gelatin, carrot, and synthetic rubber. Subjects with good



TABLE 38.

Number of chews in mastication of materials of different kinds. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Material	$n$	$M \pm \varepsilon(M)$	$\sigma$
Extremely good set of teeth: not swallowed tests			
Gelatin 10 %	41	$49.8 \pm 2.6$	16.5
» 15	41	$53.2 \pm 2.3$	14.7
» 20	41	$55.4 \pm 2.4$	15.6
Carrot	41	$41.5 \pm 2.1$	15.6
White of egg	41	$16.2 \pm 1.0$	6.5
Synthetic rubber	33	$43.6 \pm 3.2$	18.2
Indiarubber	11	$63.5 \pm 7.8$	25.9
Extremely good set of teeth: swallowed tests			
Gelatin 15 %	27	$54.3 \pm 3.8$	19.9
Carrot	28	$39.1 \pm 2.9$	15.4
White of egg	28	$12.9 \pm 0.9$	4.5
Bad set of teeth: not swallowed tests			
Gelatin 10 %	42	$47.1 \pm 3.0$	19.4
» 15 %	42	$55.4 \pm 3.2$	20.5
» 20 %	42	$58.4 \pm 3.2$	20.8
Carrot	42	$55.4 \pm 2.8$	17.9
White of egg	42	$16.4 \pm 1.0$	6.6
Synthetic rubber	36	$56.1 \pm 3.1$	18.5
Indiarubber	12	$73.1 \pm 6.9$	23.7
Bad set of teeth: swallowed tests			
Gelatin 15 %	28	$60.8 \pm 5.1$	26.8
Carrot	28	$51.7 \pm 2.7$	14.4
White of egg	29	$14.3 \pm 1.2$	6.5

teeth stop chewing synthetic rubber and carrot after a somewhat fewer number of chews than are taken for gelatin. The difference is statistically significant between carrot and 20 per cent gelatin ( $13.9 \pm 3.4$ ), and statistically probable between synthetic rubber and 20 per cent gelatin ( $11.8 \pm 4.0$ ). The figures show, however, that there is a great difference in the number of chews which different people take to chew a material. The figures seem to imply that the standard deviation is greater in poor sets of teeth than in good ones, but these differences are not statistically significant.

A comparison between the number of chews in good and bad

sets of teeth shows good agreement for white of egg (difference  $0.2 \pm 1.4$ ), indiarubber (difference  $9.6 \pm 10.4$ ), and 15 per cent gelatin (difference  $2.2 \pm 3.9$ ). A similar comparison using synthetic rubber gives a probable difference ( $12.5 \pm 4.5$ ), and only for carrot do we find a statistically significant difference ( $13.9 \pm 3.7$ ) in testing (but not in chewing and swallowing). This result, however, must be taken with a certain amount of reservation, because it has been difficult to get chewing pieces of the same size at different occasions (as a matter of fact the chewing pieces for the two groups were cut by different persons) and, furthermore, the quality of the carrots may have been different in different samples.

The investigation shows that the number of chews increases if the material is difficult to chew. We get the impression that their number is possibly slightly raised in chewing with poor sets of teeth. This question will be discussed in more detail in the following pages.

### *Chewing in testing and swallowing.*

An investigation has also been made to see whether the test subjects chewed the second and third test portion according to instructions received. A small number of persons were told to chew pieces of a certain size, consisting of gelatin, carrot, and coagulated white of egg, until the mass felt *ready* to swallow, and were also given a corresponding number of pieces to chew *and* swallow. The number of chews was counted each time. To avoid systematic errors in the number of chews the order of these two processes was varied, as also the order of the different materials of gelatin, carrot and white of egg.

Table 38 also gives figures of the difference between the average number of chews in chewed and swallowed portions on the one hand, and in only chewed portions on the other. The figures agree well.

The figures obtained in double tests have further been statistically analysed, so that the separate differences were calculated between consecutive portions. The means of the differences were then calculated. The results are shown in table 39. We can see from the figures that the number of chews in the test-chewing and in the chewing with swallowing agrees well. Statistically significant differences are found only for white of

TABLE 39.

Differences in number of chews when the pieces are swallowed and when they are chewed for testing. + means that the number of chews in swallowing is greater than the number in testing.  $n$  = number of persons.  $D \pm \epsilon(D)$  = mean of the differences  $\pm$  standard error.

Material	$n$	$D \pm \epsilon(D)$
Extremely good set of teeth		
15 % gelatin	27	$-0.8 \pm 3.6$
Carrot	28	$-2.6 \pm 1.5$
White of egg	28	$-3.5 \pm 1.0$
Bad set of teeth		
15 % gelatin	28	$+3.8 \pm 3.7$
Carrot	28	$-0.5 \pm 2.9$
White of egg	29	$-2.8 \pm 0.7$

egg: in good sets of teeth  $3.5 \pm 1.0$ , and in bad ones  $2.8 \pm 0.7$ . Though statistically significant, they are so small that they can be looked upon as having no importance. The results are surprising, as distinct differences might have been expected. With food, as we know, a person chews and swallows alternately until the mouthful has gone down. When a test portion is chewed until it feels ready to swallow, it does not get smaller during the process but, on the contrary, 'grows' in the mouth. It should therefore be difficult to determine when the chewed mass is ready to swallow — when, that is to say, one should stop chewing. The investigation indicates that, as far as the number of chews are concerned, the test subjects are not influenced by the successive diminution of what they have in their mouths in the one test, and by its successive »increase» in the other. The instructions given for mastication tests II and III seem, therefore, possible to follow correctly.

*Chewing with more or less defective set of teeth.*

It is now of great interest to discover more definitely whether, as there is most reason to expect, a deterioration in the number of teeth and a decrease of occlusion contacts lead persons to compensate for poor powers of mastication by chewing a larger number of times.

TABLE 40.

Number of chews in grown-up men in mastication of test portions. Distribution with regard to sets of teeth in varying condition. (Cf. Table 17.)

$n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

$\sigma$  = standard deviation.

Set of teeth	$n$	Mastication test					
		I		II		III	
		$M \pm \varepsilon(M)$	$\sigma$	$M \pm \varepsilon(M)$	$\sigma$	$M \pm \varepsilon(M)$	$\sigma$
Group I: extremely good	63	$60.0 \pm 3.1$	24.6	$63.2 \pm 3.1$	26.9	$68.6 \pm 3.4$	27.2
» II: good	60	$60.2 \pm 3.7$	28.5	$65.1 \pm 3.9$	30.6	$66.9 \pm 3.7$	28.7
» III: bad	51	$61.5 \pm 3.3$	23.6	$71.8 \pm 3.8$	27.4	$70.7 \pm 3.6$	25.5
» IV: extremely bad	55	$65.5 \pm 4.5$	33.1	$65.0 \pm 4.3$	32.0	$65.2 \pm 3.7$	27.3
» I—IV:	229	$61.6 \pm 1.8$	27.8	$66.2 \pm 1.9$	29.5	$67.8 \pm 1.8$	27.3
» I—IV: mastication test II + III: $n = 458$ ; $M = 67.0 \pm 1.3$ ; $\sigma = 28.4$							

The number of chews has therefore been counted in each test in the whole of the investigation material, and the average number of chews is given in the statistical treatment of the first, second, and third tests in the groups I, II, III, and IV. This makes it possible to compare the number of chews in children and adult and old men and women, with good and bad sets of teeth. As has been said before, the persons investigated were given standardized portions to chew. The instructions which were given in the mastication tests, and which were described in Chapter 9, signified that the first portion (in subsequent tables denoted test portion I) is chewed as the subject chooses, the second and third portions (II and III) are chewed until they feel ready for swallowing in the same way as if they were food.

Table 40 gives a survey of the average number of chews taken for standardized portions in tests I, II and III, by 229 conscripts and older mobilized classes with extremely good, good, bad, and extremely bad sets of teeth.

The figures show that there is remarkable agreement in the average number of chews in different sets of teeth, i. e. between the groups I, II, III, and IV. For test III, the difference in the average number of chews between groups I and IV is  $3.4 \pm 5.0$ . The figures show, further, that there is great variation in the number taken by different persons for the standardized portion. The values for the standard deviation and the variation

TABLE 41.

Number of chews in grown-up women in mastication of test portions. Distribution with regard to sets of teeth in varying condition. (Cf. Table 17.)  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	Mastication test					
		I		II		III	
		$M \pm \varepsilon(M)$	$\sigma$	$M \pm \varepsilon(M)$	$\sigma$	$M \pm \varepsilon(M)$	$\sigma$
Group I: perfect	61	$63.3 \pm 2.8$	22.0	$54.8 \pm 3.2$	24.8	$55.1 \pm 2.9$	22.4
"  II: very good	76	$63.9 \pm 3.1$	26.9	$59.0 \pm 2.4$	20.8	$58.8 \pm 2.5$	21.8
"  III: bad	50	$67.0 \pm 3.8$	27.2	$58.3 \pm 3.6$	25.3	$58.6 \pm 3.3$	23.4
"  IV: extremely bad	50	$77.0 \pm 4.6$	32.8	$61.5 \pm 3.3$	25.5	$62.0 \pm 3.6$	25.3
"  I-IV:	237	$67.2 \pm 1.8$	27.7	$58.3 \pm 1.5$	23.5	$58.5 \pm 1.5$	23.2
"  I-IV: mastication test II + III: $n = 474$ ; $M = 58.4 \pm 1.1$ ; $\sigma = 23.4$							

coefficient nevertheless agree well in a comparison between sets of teeth of different types. The differences for the standard deviation between the groups are not statistically significant.

Table 41 gives figures of the average number of chews taken by 237 adult women. As with the men, we find the mean number of chews in the groups I, II, III, and IV agreeing well. If we take, for comparison purposes, mastication test III, where the second chewing is continued till the portion feels ready to swallow, we find that the women have, on the average, chewed a rather fewer number of times than the men (cf. Table 40). The differences are small, however, and they are not quite statistically significant. For group I the difference is  $13.5 \pm 4.5$ , for group II  $8.1 \pm 4.5$ , for group III  $12.1 \pm 4.9$  and for group IV  $3.2 \pm 5.2$ .

As, in both cases, the mastication tests have been made with standardized portions, the author expected to find statistically significant differences with, on an average, more chews for the women, since anatomical and perhaps conventional reasons make it more likely that they should be in the habit of taking smaller mouthfuls. A large mouthful needs more chewing than a small one, and the standardized test portions do constitute a relatively large mouthful, for the investigated women.

The result obtained in the investigation of the number of chews in adult women backs up the conclusion that, in food moderately





may be justified in lumping together the results from the different groups, which figures are also given in the tables.

It is now of interest to compare mastication test I with tests II and III. As has been said before, in the first test the subject was allowed to chew as he liked. In II and III he was told to chew the portion till it felt ready to swallow. Under such circumstances we may expect differences between the first test and the other two. A difference of this kind is not found for adult men. For adult women there is a small difference, which is all the same statistically significant (difference  $8.8 \pm 2.1$ ); older women, on the other hand, only show a probable difference: here, the material is smaller, and the standard error larger (difference  $9.6 \pm 3.8$ ). For older men we find a very pronounced difference (difference  $27.3 \pm 3.8$ ). As has been said before, these latter had been admitted to workhouses, and were therefore to a certain extent accustomed to act on orders; in a number of cases the author was able to see how they patiently went on and on chewing, waiting for permission to spit the mouthful out. This fact probably explains the great deviation. If, finally, we look at the children, we find a statistically significant difference among the 13-year-olds. The first test has been better chewed (difference  $6.5 \pm 2.1$ ). For 7-year-olds, on the other hand, there is good agreement; at this age, they have obviously not let their habits be disturbed just because they were being subjected to a test, which must, to a certain extent, seem a bit of a strange one.

#### *Chewing in regard to age and sex.*

It is now of interest to try, by using the lumped together material, to see whether it has been possible to find minor differences between the groups investigated. If we, then, in the first place compare adult men and women, we find a small statistically significant difference (difference  $8.6 \pm 1.7$ ). On the other hand, if we compare older men with younger men, and older women with younger women, we find neither significant nor probable differences. If, finally, we compare 13-year-olds with adult men, we get a statistically significant difference (difference  $11.2 \pm 1.7$ ), but there is no difference in a comparison with adult women. An interesting thing is that 7-year-olds chew a smaller number of times than either adult men or women; yet the difference compared with the latter is statistically significant (dif-



ference  $8.7 \pm 1.6$ ). Finally, the difference between 13-year-old and 7-year-old children is statistically significant, amounting to  $6.1 \pm 1.6$ . This possibly indicates that the chewing habits, which must of course be formed during childhood have not yet become fully fixed at the age of 7. It may be that 7-year-olds adapt themselves to the character of the food to be chewed more than is the case later in life. At any rate it can be affirmed that 7-year-olds chew more 'carelessly' than do those who are older.

When comparing children and adults it must be remembered that the children were tested with a smaller test portion. To get an idea of the influence of this factor, special tests on adults have been carried out. The same person has been tested with test portions of both sizes. In 30 cases the average difference between these two tests is found to be  $12.6 \pm 1.5$  chews, or 19.4 per cent. This is almost exactly the same difference as between 13-year-olds and adult men. Therefore, if allowing for the difference in the size of the tests portions, there is no reason to assume any difference between 13-year-olds and adults. The difference between children of 7 and 13 years of age, however, stands, as they have been tested with test portions of the same size.

From a theoretical point of view it is of course to be expected that the size of the test portions should have a certain influence which the author previously has pointed out. It has not been possible to enlarge the investigation by going deeper into this problem.

Our concern is, now, to get an idea of the variability. To say that people have different habits is easy enough. One chews a few times and eats quickly and 'carelessly', the other chews long and hard and eats slowly. There is actually great variability also. For adult men, it amounts to  $28.4 \pm 0.91$  chews, i. e. to 42.4 per cent. It is somewhat smaller in adult women, being  $23.4 \pm 0.76$  chews, i. e. 40.0 per cent. The difference between the standard deviations is statistically significant. In both materials, however, the standard deviation is so great that the distribution must be skew. (It can, of course, never vary further below the mean than to nearly 0 chews.) A survey is therefore given in Table 46 of the distribution in adult men and women for the different teeth groups. The distribution shows that there are no values beyond  $2 \sigma$  below the mean; above it, however, the range of variation approaches  $3.5 \sigma$ . In other words, the distribution is moderately

TABLE 46.

Distribution of number of chews in grown-up men and women (groups with different sets of teeth are joined). The class interval is for men:

$0.5 \sigma = 13.7$  chews; for women:  $0.5 \sigma = 11.6$  chews.  $M$  = mean.

$\sigma$  = standard deviation.

Sex	— $M$ +											Total
	$2\sigma \leftarrow$	$1.5\sigma \leftarrow$	$1\sigma \leftarrow$	$0.5\sigma \leftarrow$	$\rightarrow 0.5\sigma$	$\rightarrow 1\sigma$	$\rightarrow 1.5\sigma$	$\rightarrow 2\sigma$	$\rightarrow 2.5\sigma$	$\rightarrow 3\sigma$	$\rightarrow 3.5\sigma$	
Men:												
Number	8.0	28.8	49.2	39.2	36.8	29.2	15.1	11.7	8.0	3.0	.	229
%	3.5	12.6	21.4	17.1	16.1	12.8	6.6	5.1	3.5	1.3	.	100.0
Women:												
Number	4.0	27.7	54.6	45.8	45.7	24.4	16.6	5.6	5.6	5.0	2.0	237
%	1.7	11.7	23.0	19.3	19.3	10.3	7.0	2.4	2.4	2.1	0.8	100.0

skew. Under such circumstances, it is possible to say that the number of chews varies around 60—70 in adult men and women, and that the range of variation goes down to 12—15, and up towards 140—165. The figures thus show that there is very great variation in the chewing habits which characterize different persons. We get a similar variation range for children and old people, also. The variation coefficient keeps at 30—35 per cent. In consideration of the fact that 7-year-olds chew, on an average, a fewer number of times than other groups, it is interesting to find that the standard deviation expressed in number of chews is appreciably smaller for them than for the others. The decrease is fairly proportionate to the decreased average number of chews, so that the variation coefficient amounts to 32.1 per cent.

#### *Individual and interindividual variability.*

With the great variability in chewing habits as a background, we are now motivated in investigating how far we really are dealing with stabilized habits. A habit of chewing in a certain way can be more or less firm. An individual can, on an average, tend to chew a certain number of times, but this does not prevent him from chewing one and the same substance rather more one time, and rather less another. A gauge of the individual variation is obtained from the differences between mastication tests II and III, which were, as we know, made in the same way. The result

TABLE 47.

Average difference ( $M$ ) and standard error ( $\epsilon$ ) between number of chews in grown-up men and women in mastication tests II and III, and from the differences calculated standard deviation ( $\sigma_i$ ) and variation coefficient ( $V$ ) for a single individual. — means, that the number of chews in mastication test II is smaller than the number in mastication test III.

$n$  = number of persons.

Sex	$n$	$M \pm \epsilon(M)$	$\sigma_i$	$V$
Men	229	$-1.64 \pm 1.05$	11.3	16.9
Women	237	$-0.19 \pm 0.71$	7.7	13.3

of calculations based on these differences will be found in Table 47.

The table shows there to be no statistically significant differences between the second and the third test portion. It can further be seen that the individual variation is considerably less than the one distinguishing adult men and women. For men it is  $11.3 \pm 0.53$  chews, and for women  $7.7 \pm 0.35$  chews. This actually means that an individual can vary to a certain extent in his chewing from one time to another. Compared with the great variation characterizing the population, however, the individual variation may be termed small. There is, incidentally, a minor difference between men and women, which is statistically significant. It amounts to  $3.6 \pm 0.64$ .

To get a more definitive idea of the relation between the total variation and the variation in the course of individual mastication, we make a division according to G. DAHLBERG (1926), using the formula  $\sigma_t = \sqrt{\sigma_i^2 + \sigma_p^2}$  where  $\sigma_t$  = the total standard deviation,  $\sigma_i$  = the individual standard deviation obtained from differences between two tests, and  $\sigma_p$  = the interindividual standard deviation which is to be calculated. We then find that the variability that remains after subtracting the individual variation amounts to  $26.1 \pm 1.7$  for men, and to  $22.1 \pm 1.4$  for women. This implies that the great variation in the number of chews which is found in a population is in very small measure conditioned by the individual way of chewing a different number of times on different occasions. It is conditioned in considerable measure by different chewing tendencies in different persons. In other words, we are fully justified in talking of quite firm chewing habits;

the difference between different individuals as regards this is very great — perhaps greater than might beforehand be expected.

It now remains to compare the variation in the whole population with the variation distinguishing the different teeth groups. A comparison for men (Table 40) and women (Table 41) shows good agreement between the standard deviation for the lumped together material and that for the different teeth groups. There are no statistically significant differences anywhere. This agrees with what was advanced by way of introduction — namely, that if the number of chews is determined by personal habits, the same variation should be obtained when persons are investigated with sets of teeth of a certain type, as when material is investigated with sets of teeth of varying types. If the number of chews was influenced by the degree to which the mouthful is reduced, tests should reveal greater variability in a population composed of persons with sets of teeth of very varying type than in a narrow class of persons with similar sets of teeth.

By way of *summary* it may be said that a statistical treatment of the material has showed there to be fixed habits as to the number of times a mouthful is chewed, which habits are admittedly influenced by *great* differences of consistency in different food substances, but are not noticeably affected, by deterioration in the set of teeth brought about by partial or total losses. The mastication habits do not seem to be fully formed by the age of 7, but they remain stable at any rate from 13 up to a considerable age. Differences can be found between men and women, but they are very small ones. An individual varies somewhat in his chewing, but this variability is small compared with the one conditioned by the dissimilarity between the members of a population. Here, one person may be content with a few chews before he is ready to swallow, while another chews extremely carefully and for a long time before he has finished with his mouthful. Finally, it has been found that the variation in the number of chews between people with sets of teeth of the same type, is as great as the variation in the total population, where the sets of teeth also vary to a high degree.

## Chapter 13.

### The average reduction of the test portion in persons of different age and sex, and with different sets of teeth.

After having investigated the number of times persons with complete and with more or less defective sets of teeth chew the standardized test portion, it remains to attempt an analysis of the effect of the chewing. It is then of primary interest to try and get, by means of mastication coefficients, an idea of the average masticatory effectivity in groups of persons with different sets of teeth.

In an account of the masticatory effectivity, it would be natural to begin with children and then pass on to adult and old persons. Earlier in this work, the author has dealt with adult men and women first, as these groups are relatively large and can be regarded as representative. In other words, they constitute a suitable starting-point for a comparison with children and old people. In the following account, therefore, the investigation material will be treated in the same order.

The mastication coefficient suggested in this work is based on the assumption that the irregularly shaped particles correspond to regular polyhedrons. It is true that, on special investigation, the assumptions made have proved fairly correct, but as there is nevertheless a certain element of uncertainty in the conditions on which calculations of the mastication coefficient are based, tables of the distribution of the fractions are given in the first place.

#### *Mastication effect in adult men and women.*

Figures of the average distribution of the *fractions* in adult men with extremely good, good, bad and extremely bad sets of teeth are given in Table 48. The values give the size of the fractions obtained in chewing till the mouthful feels ready to swallow.

TABLE 48.

Average distribution of the fractions in grown-up men and women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

Fraction	Set of teeth			
	Group I: extremely good	Group II: good	Group III: bad	Group IV: extremely bad
	$M \pm \varepsilon(M)$	$M \pm \varepsilon(M)$	$M \pm \varepsilon(M)$	$M \pm \varepsilon(M)$
M e n				
1	$2.13 \pm 0.19$	$0.92 \pm 0.07$	$0.59 \pm 0.05$	$0.61 \pm 0.06$
2	$4.03 \pm 0.26$	$2.15 \pm 0.16$	$1.33 \pm 0.10$	$1.24 \pm 0.11$
3	$4.44 \pm 0.19$	$3.18 \pm 0.19$	$2.26 \pm 0.15$	$1.98 \pm 0.14$
4	$65.54 \pm 3.10$	$63.35 \pm 3.25$	$51.06 \pm 3.38$	$42.75 \pm 2.67$
5	$28.60 \pm 1.35$	$35.40 \pm 1.36$	$33.43 \pm 1.42$	$29.15 \pm 1.41$
6	$11.52 \pm 0.82$	$18.23 \pm 0.80$	$20.22 \pm 0.97$	$20.09 \pm 0.98$
7	$5.43 \pm 0.57$	$8.65 \pm 0.59$	$11.39 \pm 0.60$	$12.25 \pm 0.67$
8	$2.32 \pm 0.33$	$4.85 \pm 0.48$	$6.14 \pm 0.47$	$5.96 \pm 0.41$
9	$1.11 \pm 0.18$	$1.98 \pm 0.24$	$2.57 \pm 0.31$	$2.82 \pm 0.26$
10	$0.79 \pm 0.22$	$1.55 \pm 0.26$	$1.75 \pm 0.31$	$2.71 \pm 0.40$
	$n = 63$	$n = 60$	$n = 51$	$n = 55$
W o m e n				
1	$2.15 \pm 0.13$	$1.31 \pm 0.09$	$0.88 \pm 0.09$	$0.74 \pm 0.06$
2	$3.74 \pm 0.16$	$2.56 \pm 0.14$	$1.81 \pm 0.15$	$1.47 \pm 0.10$
3	$4.03 \pm 0.11$	$3.28 \pm 0.14$	$2.59 \pm 0.14$	$2.25 \pm 0.12$
4	$61.87 \pm 2.13$	$56.46 \pm 2.01$	$48.76 \pm 2.52$	$46.62 \pm 2.33$
5	$29.36 \pm 1.25$	$30.63 \pm 0.94$	$31.72 \pm 1.32$	$34.48 \pm 1.38$
6	$11.41 \pm 0.58$	$14.30 \pm 0.58$	$16.38 \pm 0.68$	$18.60 \pm 0.78$
7	$5.72 \pm 0.45$	$7.59 \pm 0.41$	$9.50 \pm 0.62$	$9.22 \pm 0.45$
8	$2.39 \pm 0.30$	$3.55 \pm 0.32$	$4.96 \pm 0.45$	$4.92 \pm 0.39$
9	$1.02 \pm 0.16$	$1.78 \pm 0.20$	$2.32 \pm 0.29$	$2.10 \pm 0.24$
10	$0.33 \pm 0.12$	$1.51 \pm 0.24$	$1.88 \pm 0.28$	$2.12 \pm 0.29$
	$n = 61$	$n = 76$	$n = 50$	$n = 50$

The tables show that the number of particles in the fractions increases throughout from the coarse strainers to the finer ones. In good sets of teeth, the average number in a fraction with strainerholes of 10 mm. in diameter amounts to 0.8, and with holes of 1 mm. in diameter it is 1161. In extremely bad sets of teeth, the average number of particles in the same fractions is 2.7 and 327. (The number of particles in the finest fractions is calculated from standard values for the sedimented volume.) In a comparison of the distribution of the fractions in sets of teeth of varying natures, we find that the number of particles in the

fraction with holes of 5 mm. in diameter keeps fairly constant at something over 30 (29—35 particles). In the fractions in the strainers above No. 5 (coarser fractions), the average number of particles increases as the sets of teeth get worse. The opposite is the case in the finer fractions on strainers underneath No. 5.

Table 48 also gives figures of the average distribution of the fractions for adult women. A comparison with the average distribution of the fractions for adult men shows fairly good agreement of the values for the number of particles and sedimented volume. In extremely good sets of teeth, the average number of particles in a fraction with strainer-holes of 10 mm. in diameter is 0.4, and where the holes are 1 mm. in diameter, 1176. In extremely bad sets of teeth, the average number in the same fractions is 2.1 and 381. In women, too, the number of particles when the diameter of the holes is 5 mm. keeps round about 30 (29—34).

As the test portion is divided into 10 fractions in strainers with holes from 1—10 mm. in diameter, the difference in the size of the particles in neighbouring fractions will be small. Irregular particles, with different diameters in different planes, may therefore to a certain extent just happen to land up in a strainer above or below the one where they actually belong. Special experiments have been made with re-straining of previously strained portions, where the fractions were stained red and blue alternately. After re-straining, the fractions were found containing a slight proportion of particles of the other colour. We have therefore to take into consideration that, statistically speaking, the values for the different fractions should have not inconsiderable standard errors; this can also be seen from the standard errors, given in the tables, which are calculated from the distribution. However, we also have to reckon with a correlation between the differences between neighbouring strainers, in that, if by chance the number of particles on a certain strainer is small, this is due to their happening either to remain to a particularly large extent in the preceding strainer, or to pass through into the following one. A low value obtained by chance is therefore negatively correlated with the values in surrounding strainers. The impression of an element of uncertainty given by the standard errors in the separate fractions, is therefore somewhat misleading in so far as, if it is possible to reach a uniform expression for the degree of reduction for the entire test portion, the standard error of this value should be considerably smaller than

that of the separate fractions would seem to suggest. It is, further, difficult to reach some idea of the degree of reduction from the varying values for the different fractions. It is necessary in a comparison to keep in mind ten pairs of values. This, as has been said before, is one of the author's motives in working out a mastication coefficient, which has the advantage both of giving a simple expression for the degree of reduction, which considerably facilitates comparison, and also of making it possible to calculate standard errors that correctly express the circumstances, without having laboriously to calculate correlations between the standard errors of the different fractions, and try to make these into one. To make it possible to assess the reduction of the test portion and to compare the effect of mastication in different sets of teeth, mastication coefficients have been calculated from the mean values of the sizes of the fractions. Table 9 gives the values of surface and volume, and also of surface per volume unit, calculated from the mean values for the number of particles and the sedimented volume for adult men and women with extremely good, good, bad and extremely bad sets of teeth.

As has been said before, the table shows the calculated volume to agree fairly well with the known volume of the test portion. The standard deviation amounts to about 10 per cent. With the help of the values for the calculated surface and volume, it is possible to express the results in the following way. The values for the *mastication coefficient* show particles in a test with extremely good sets of teeth to have an average surface of 239 sq. cm., in good ones, 184 sq. cm., in bad ones, 163 sq. cm., and in extremely bad ones, 157 sq. cm. A calculation further shows that, in extremely good sets of teeth, the surface of a test portion is on an average increased by 11 times its original dimensions, in good sets by 8 times, in bad sets by 7 times, and in extremely bad sets by 6.8 times. The results are rather astonishing. The author has at any rate been surprised to find, on the one hand, that chewing the test portion gives such high values for its surface, and, on the other, so small a difference in surface between chewing in good, bad, and extremely bad sets of teeth, while extremely good sets, on the contrary, deviate considerably. The differences computed for 1 c. cm. of the test portion are 5.5 sq. cm. between extremely good and good sets of teeth, 2.1 sq. cm. between



TABLE 49.

Means of individual mastication coefficients in grown-up men and women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

Set of teeth	Men		Women	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
Group I: extremely good	63	$24.48 \pm 0.89$	61	$24.33 \pm 0.61$
» II: good	60	$18.26 \pm 0.47$	76	$20.22 \pm 0.46$
» III: bad	51	$16.43 \pm 0.39$	50	$17.82 \pm 0.53$
» IV: extremely bad	55	$15.77 \pm 0.45$	50	$17.16 \pm 0.37$
» I—IV:	229	$18.97 \pm 0.38$	237	$20.13 \pm 0.31$

good and bad sets, and 0.6 sq. cm. between bad and extremely bad sets.

The values for the mastication coefficient that have hitherto been discussed are based on a calculation of the means for fractions with the help of the formulas for volume and surface given in the method. More exact values are obtained, however, if the mastication coefficient for each individual is calculated and the series thus obtained used to compute the means for the different sets. As it is possible when carrying out these calculations to get standard errors for the means, and also figures for the standard deviation and the variation coefficient, the rest of the tables will show exclusively figures calculated on the individual values.

The means for adult men and women, calculated from the individual mastication coefficients, are given in Table 49.

We find good agreement between the values in the table and the mastication coefficient values obtained by a calculating of the means for the fractions (cf. Table 9). But we cannot expect to find them agreeing completely. We have to reckon with chance deviations, as well as systematic deviations due to correlations between volume and surface in separate individuals. As a comparison between the mastication coefficients calculated in different ways shows, these deviations are nevertheless small, and lie within the limits for the standard error.

The figures also show that there are statistically significant differences between the mastication coefficients for the groups of extremely good, good and bad sets of teeth. The difference between the first two for adult men is considerable, amounting to

about a quarter, ( $6.22 \pm 1.01$ ), of the reduction in extremely good sets. Between good and bad sets, the difference drops to a tenth of the portion's surface in good sets, and between bad and extremely bad sets, finally, the difference is negligible, namely  $0.66 \pm 0.69$ .

The figures for adult men seem to show that the difference between the sets of teeth becomes smaller, the more defective the set. A comparison between the values for the average mastication coefficients for adult men and women shows excellent agreement in a good set; the coefficients in other groups, on the other hand, show higher values for women than for men throughout. The differences are not statistically significant, however. For adult women, too, we find the differences successively diminishing, the worse the set of teeth becomes, though there is less difference between extremely good and good sets, and more between good and bad sets, than in adult men.

The differences thus seem to imply that, with the class division used by the author, there is a distinct difference in masticatory effectivity between good sets of teeth on the one hand, and more defective sets on the other. This is supported by the fact that the differences between the variously good sets are similar in both men and women. It is impossible to say definitely, on the strength of the figures communicated, that the size of the differences is not conditioned by chance to a certain extent, since their standard errors are great. It may, of course, be chance that the difference between extremely good and good sets of teeth has become particularly large in men, nor does the smaller difference for women argue against this possibility. As will be shown later, the same distribution of the magnitude of the differences is not found in older persons.

As, on account of the means and the standard errors for the coefficients, we cannot definitively assess the successive decrease of the differences between the different sets of teeth, we shall briefly discuss the differences between the classes when divided according to the condition of the teeth, to see whether we can find any pointer here. Statistical viewpoints have decided this division, the class limits being so chosen that approximately the same number of individuals was contained in each. The mean values of the points for pairs of teeth in occlusion in the different sets are given in Chapter 11. The figures in Table 17 show that for men the difference in points between the average for extremely good and good sets is 5.97, between good and bad

sets, 3.45, and between bad and extremely bad sets, 4.17. This shows that there is a relatively smaller difference in the number of points between good and bad sets of teeth, while the differences between the other classes are larger. The class limits used, then, can scarcely explain the successive diminution in the differences between the masticatory effectivity in the different groups. It has not yet been proved beyond dispute, however, that the differences actually do take such a course, and the question must be left open for the time being.

If we now compare the number of points and the mastication coefficient values in the extreme teeth groups, we find, that, for adult men, the number of points sinks from, on an average, 18.54 to 4.95, and for women from 17.87 to 5.06. Thus, the extremely bad set of teeth proves to have 26.7 per cent of the good set's occlusion contacts in men. For women the corresponding figure is 28.3 per cent. The corresponding figure for the occlusal surface is 35.7 per cent for men and 35.2 per cent for women. A corresponding calculation, made on the mastication coefficients for the different sets of teeth in adult men, shows that the extremely bad set has 64.4 per cent of the effect in a good set. For adult women the figure is 70.5 per cent. Thus we can see that there is apparent lack of proportion between the deterioration, on the one hand of the set of teeth, and on the other of the masticatory effectivity.

The successively decreasing masticatory effectivity in defective sets of teeth, which thus is not directly proportionate to their deterioration, might, perhaps, be attributed to a compensatory increase in the number of chews. It has been shown earlier on, however, that this is not the case. The possibility then remains of explaining the decrease by ascribing the relatively good masticatory effect in defective sets of teeth to a certain extent to compensation through more skilful management of the mouthful. Especially might it be suspected that incisors are used more extensively when the grinding teeth are bad.

#### *Mastication effect in old men and women.*

It is now of interest to investigate the masticatory effectivity in older men and women. The means for computed individual mastication coefficients are given in Table 50.

A comparison of the figures in the table with those for adult

TABLE 50.

Means of individual mastication coefficients in older men and women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17.  $n$  = number of persons.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

Set of teeth	Men		Women	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
Group I: extremely good	15	$36.05 \pm 1.79$	10	$28.70 \pm 2.84$
> II: good	24	$28.40 \pm 2.15$	17	$24.06 \pm 1.48$
> III: bad	19	$26.19 \pm 2.39$	12	$21.44 \pm 1.52$
> IV: extremely bad	43	$20.92 \pm 0.80$	11	$18.48 \pm 1.62$

men shows the masticatory effectivity for the older men investigated to be remarkably high, and the coefficients in extremely good, good and even bad sets of teeth are higher than the corresponding values for adult men. The differences between older and younger adult men are statistically significant and amount to  $11.57 \pm 2.00$  in extremely good sets of teeth, and  $5.15 \pm 0.92$  in extremely bad ones.

The good masticatory results are not, however, due to the older men chewing a larger number of times. It has earlier on been shown that this is not so (cf. Chapter 12). In trying to explain these good results, an important circumstance may be that the older men investigated had abraded teeth to a very large extent. All abrasion was recorded at the investigation. In so doing, two degrees were differentiated: distinct abrasion, where the cusps were plainly worn down without, however, the tooth surface being completely plane, and pronounced abrasion, when the tooth surface was plane and the height of the tooth somewhat decreased from being worn away. Further details of the distribution for these different classes are not likely to be of interest; the author contents himself with the statement that, with extremely good sets of teeth distinct or pronounced abrasion is found in 100 per cent of the cases, with good sets in 83 per cent, with bad sets in 68 per cent, and with extremely bad sets in 73 per cent. We might now think that the abrasion of the tooth surfaces might explain the good masticatory results, since the abrasion means that such pairs of teeth as exist are ground down to match one another. In comparing the values for the occlusion surface between younger adult and older men (cf. Tables 18 and

26 in Chapter 11), also, we find that the average difference in a good set of teeth is  $96.4 \pm 27.0$  sq. mm. — a considerable difference.

Here, too, we find a lack of agreement between the deterioration of the set of teeth on the one hand, and the decrease in the masticatory effectivity on the other. A calculation shows that the extremely bad set of teeth has 77.5 per cent of the extremely good set's lower occlusion contacts, while its mastication coefficient, on the other hand, is 42 per cent lower than that of the extremely good set. The per cent figures tally fairly well with the figures for adult men and women, a fact which certainly goes towards endorsing the results.

Table 50 shows, further, that in a comparison between the figures for older and younger adult women, the former show higher mastication coefficients for the different sets of teeth. The differences are, however, small, and not statistically significant. Between older and younger adult women, the difference in extremely good sets of teeth is  $4.37 \pm 2.91$ . We also find that, for older women, there is no statistically significant difference between the different groups. The greatest difference is between extremely good and good ones ( $4.61 \pm 3.20$ ), and this is not statistically significant. The number of older women investigated is small, however, and the standard errors for the different groups of teeth are consequently great. On account of this the size of the difference is very subject to chance, which means that the different groups can lead us to no definitive conclusions. All the same, the difference between an extremely good set of teeth and an extremely bad one is statistically significant, and amounts to  $10.22 \pm 3.27$ .

#### *Mastication effect in children.*

It now remains to investigate the masticatory effectivity in children. Table 51 gives the means for the calculated individual mastication coefficient for 7-year-old and 13-year-old girls and boys. The differences between the different teeth groups are, as in adult men and women, statistically significant.

The values for the mastication coefficient for 13-year-old girls and boys are higher than for 7-year-olds and adults. The differences are small, however, and the difference in good sets of

TABLE 51.

Means of individual mastication coefficients in seven-year-old and thirteen-year-old children, divided into groups with sets of teeth in varying condition. Regarding class limits, see Tables 32 and 36.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

Set of teeth	$n$	$M \pm \varepsilon(M)$
Seven-year-old children		
Group I: extremely good	8	22.25
» II: good	29	$20.77 \pm 0.77$
» III: bad	35	$16.59 \pm 0.50$
» IV: extremely bad	28	$15.13 \pm 0.45$
Thirteen-year-old children		
Group Ia: perfect	18	$26.28 \pm 1.42$
» Ib: very good	36	$25.05 \pm 0.80$
» II: good	37	$22.15 \pm 0.63$
» III: bad	9	19.59

teeth not statistically significant. The difference between 13-year-olds and 7-year-olds is  $1.38 \pm 0.99$ .

A calculation of the difference in number of contacts between extremely good and extremely bad sets of teeth shows a deterioration of the set by 65.2 per cent for 7-year-olds, and by 49.7 per cent for 13-year-olds. A calculation of the difference in the masticatory effectivity from extremely good to bad sets yields 32.0 for 7-year-olds, and 25.5 for the others.

We find in children, as in the groups investigated earlier, a difference between good and bad sets of teeth as regards the mastication coefficient, which, in relation to the difference in the set in respect of grinder contacts, is comparatively small.

When comparing the mastication coefficient for children with the one for adults it must be remembered that for children a smaller test portion has been used than for adults. In 15 adults, special tests have been made. Each subject has been tested with the larger (10.6 c. cm.) and the smaller (7.4 c. cm.) test portion. When this first was done the persons were told to chew 60 times. The mean of the differences between the mastication coefficients was found to be  $3.01 \pm 0.52$ . In other words, there was a significant difference, the mastication coefficient being higher for the smaller test portion. It should be remembered that, when the test portion

is larger, the number of chews increases. Possibly, this increase causes the difference to disappear. Therefore, the same tests has been made on the 15 persons, when they were allowed to chew until they felt ready to swallow. In this case the mean of the differences was  $0.39 \pm 0.55$ . The small increase in the mastication coefficient was not significant, and in fact, the agreement may be said to be good. Of course a small significant difference may be found in a larger material, but, in any case for the test used, the difference because of the size of the test portions cannot be very important. Therefore, we may compare the mastication coefficients for children and adults.

The figures show that the values for the mastication coefficient for 7-year-old children agree fairly well with those for younger adult women and men alike. Only for extremely bad sets of teeth a significant difference was found when comparing with women. (Difference  $2.03 \pm 0.58$ .) In regard to 13-year-old children a significant difference was found for good sets of teeth in comparison with men; the difference was  $3.89 \pm 0.79$ . In comparison with women no significant difference was found. Anyhow there seem to be no very important differences between children and adults.

*Summing up*, then, it may be said that an investigation of the masticatory effectivity with the help of the mastication coefficient has showed clear average differences between adult men and women in groups with varying sets of teeth. Similar differences have also been found in older men and women, and in children. Nevertheless, the difference in the masticatory effectivity seems throughout to be less than might be expected in the light of the different nature of the sets and the total occlusal surface. This is not due to the fact that defects in the sets are compensated by an increased number of chews, and the most plausible assumption is, that a certain compensation is achieved by a more skilful manoeuvring of the mouthful to the contacts that are left, and that incisors are used to a certain extent. It must be remembered that even in extremely bad sets of teeth the incisors are still in a comparatively good condition. (Possibly, the chewing is done harder, too.) It is furthermore striking that children and adults, whose sets of teeth have the same character, have about the same average masticatory effectivity, whereas old people in the same classes have a greater effectivity, and thus higher mastication coefficients. (It has been possible to show

this for older men. The material for older women has been too small to give statistically significant differences.) The most plausible explanation is that, on account of abrasion, the older people often have an occlusal surface which is more effective for the test material used.



## Chapter 14.

### **The variation in reduction of test portions, and its causes.**

To throw further light on the masticatory effectivity in different sets of teeth, we shall now investigate the variation. Table 52 gives the figures for standard deviation and variation coefficients computed from the mastication coefficients for different teeth groups among children, adults, and older persons.

If, as was done earlier on in the discussion of the average mastication coefficient, we now begin by investigating the variation for adults, we find it getting less from extremely good to extremely bad sets of teeth in both younger adult men and women. The differences between the extreme groups are statistically significant for both sexes. The figures in the table show that, for women, the difference for the standard deviation values between neighbouring groups is not statistically significant, apart from that between good and extremely bad sets of teeth (difference  $1.40 \pm 0.42$ ). For men, we find a statistically significant difference between extremely good and good sets of teeth (difference  $3.39 \pm 0.71$ ), but not in other groups.

Given that the range of variation for the mastication coefficient slightly decreases as the set of teeth gets worse, we might expect the variation coefficient — i. e. the standard deviation expressed in per cent of the appertaining mean — to keep more constant, since the mean for the mastication coefficients also decreases. There is, as a matter of fact, a tendency in this direction. All the same, there is a statistically significant difference in men between group I and group III, and a statistically probable one between groups I and II; otherwise, however, there are no certain differences between the variation coefficients in adult men and women. The two figure series for men and women might possibly suggest a tendency towards a falling coefficient, which would imply that the range of variation decreased relatively more than the means for the mastication coefficients; a lar-

TABLE 52.

Standard deviation and variation coefficient of the mastication coefficient. Grown-up men and women, older men and women, and seven-year-old and thirteen-year-old children, divided into groups with sets of teeth in different condition.  $n$  = number of persons.  $\sigma \pm \varepsilon(\sigma)$  = standard deviation  $\pm$  standard error.  $V \pm \varepsilon(V)$  = variation coefficient  $\pm$  standard error.

Set of teeth	$n$	$\sigma \pm \varepsilon(\sigma)$	$V \pm \varepsilon(V)$
Grown-up men			
Group I: extremely good	63	$7.04 \pm 0.63$	$28.8 \pm 2.8$
» II: good	60	$3.65 \pm 0.33$	$20.0 \pm 1.9$
» III: bad	51	$2.79 \pm 0.28$	$16.9 \pm 1.7$
» IV: extremely bad	55	$3.31 \pm 0.32$	$21.0 \pm 2.1$
Groups I—IV:	229	$5.82 \pm 0.27$	$30.7 \pm 1.6$
Grown-up women			
Group I: extremely good	61	$4.79 \pm 0.43$	$19.7 \pm 1.9$
» II: good	76	$4.02 \pm 0.33$	$19.9 \pm 1.7$
» III: bad	50	$3.74 \pm 0.37$	$21.0 \pm 2.2$
» IV: extremely bad	50	$2.62 \pm 0.26$	$15.3 \pm 1.6$
Groups I—IV:	237	$4.80 \pm 0.22$	$23.8 \pm 1.2$
Older men			
Group I: extremely good	15	$6.94 \pm 1.27$	$19.2 \pm 3.6$
» II: good	24	$10.52 \pm 1.52$	$37.0 \pm 6.0$
» III: bad	19	$10.43 \pm 1.69$	$39.8 \pm 7.4$
» IV: extremely bad	43	$5.26 \pm 0.57$	$25.2 \pm 2.9$
Groups I—IV:	101	$9.49 \pm 0.67$	$36.6 \pm 2.9$
Older women			
Group I: extremely good	10	$9.00 \pm 2.01$	$31.3 \pm 7.7$
» II: good	17	$6.10 \pm 1.05$	$25.3 \pm 4.6$
» III: bad	12	$5.25 \pm 1.07$	$24.5 \pm 5.3$
» IV: extremely bad	11	$5.37 \pm 1.14$	$29.1 \pm 6.7$
Groups I—IV:	50	$7.09 \pm 0.71$	$30.6 \pm 3.3$
Seven-year-old children			
Group I: extremely good	8	—	—
» II: good	29	$4.13 \pm 0.54$	$19.9 \pm 2.7$
» III: bad	35	$2.97 \pm 0.35$	$17.9 \pm 2.2$
» IV: extremely bad	28	$2.38 \pm 0.32$	$15.7 \pm 2.2$
Groups I—IV:	100	$5.06 \pm 0.36$	$21.3 \pm 1.6$
Thirteen-year-old children			
Group Ia: perfect	18	$6.03 \pm 1.01$	$22.9 \pm 4.0$
» Ib: very good	36	$4.82 \pm 0.57$	$19.2 \pm 2.4$
» II: good	37	$3.86 \pm 0.45$	$17.4 \pm 2.1$
» III: bad	9	—	—
Groups I—III:	100	$4.24 \pm 0.30$	$23.7 \pm 1.8$

ger material is needed before such a tendency can be established, however.

In the total material the variation coefficient for adult men is  $30.7 \pm 1.6$  per cent, and for adult women  $23.8 \pm 1.2$  per cent. For older men and women the coefficient is about 6 per cent higher than for the younger groups, and for children about the same as for adult women. Our next concern is to get some idea of why we obtain such varying values. Obviously, a fundamental reason must be that people chew different numbers of times. It has been shown earlier on that there is great variability in this respect; people chew their food for different lengths of time, and with different degrees of conscientiousness. Some people are content with a few chews, others take many. There is, further, a variability in so far as one person does not always chew in exactly the same way; but, as has already been shown, this variability is not very great.

Another obvious reason for variation is that the sets of teeth in a group vary somewhat in character. This tendency has been illustrated in more detail previously (Chapter 11). We have not been able to compare more homogeneous sets, as the material in the different classes would then have been very small.

A minor source of variability is that the method used to reach the mastication coefficient by means of straining is not absolutely exact, but has a standard error. The variation due to error of measurement is very slight, however. It is, of course, possible to discuss a number of other factors that certainly have some small importance, e. g. there is no doubt that a varying degree of abrasion plays a part, above all in older persons. Other examples are different-sized teeth in different individuals, which give a varying effective occlusal surface and, further, a more, or less, satisfactory occlusion. Of course anatomical differences of various kinds must be of importance, and especially it must be remembered that people with malocclusion are included in the material. Later on we shall be paying particular attention to this group, but we will say here and now that individuals with pronounced malocclusion are far too few to play any very great part. Finally, there is the possibility of varying degrees of skill, in particular on the part of persons with defective sets of teeth, in manoeuvring the mouthful to those places with the best mastication effect; we can also reckon with some people chewing harder than others.

If we look at the figures showing the standard deviation for older men, we find small but significant differences between extremely bad sets of teeth on the one hand, and good and bad sets on the other. The group with extremely good sets of teeth comprises few individuals only, so that no difference between it and other groups can be established. The material for older men is, on the whole, not as large as for adult men, and we are therefore not surprised at being unable to make out a definite trend in the figures. The material for older women is still smaller, so that it is natural that we should not find significant differences or definite tendencies here, either. If we look at the variation coefficients, we find no significant differences anywhere.

A comparison with adult men shows greater range of variation in older men, however, and greater variation coefficients. Nevertheless, differences can be proved only in certain groups, namely those for old men with bad and extremely bad sets of teeth. For good sets, the difference is probable. It is true that, for the old women, we get throughout higher figures than for the younger ones; but the groups are too small to give significant differences. As has already been mentioned, the total groups have significant differences between the age groups for both men and women ( $3.67 \pm 0.72$  for men,  $2.29 \pm 0.71$  for women).

If we then look at the children, we find no statistically significant differences between the groups for the 13-year-olds. The figures do have a tendency to a diminishing range of variation, which also seems reflected in the variation coefficients, without, however, the difference being significant here. In the 7-year-olds, we find practically significant differences between good and extremely bad sets of teeth (difference  $1.75 \pm 0.63$ ), and a shift in the variation coefficients towards lower values in more defective sets, which, however, is not statistically significant but may conceivably have arisen at random.

If, finally, we compare the variability in children with that in adults, we find no striking difference. The difference between 13-year-olds and adult men is nevertheless significant ( $1.58 \pm 0.40$ ).

*Summing up* with regard to the variability in masticatory effectivity, we may say that this is by no means inconsiderable in groups with more or less similar sets of teeth, and that the variation coefficient keeps, on the whole, between 20 and 30 per cent, being apparently somewhat larger in good sets, and somewhat lower in bad ones.

TABLE 53.

Mastication coefficients in tests with 20 chews and 40 chews respectively. Grown-up men and women, divided into groups with sets of teeth in different condition.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	n	20 chews		40 chews	
		$M \pm \varepsilon(M)$	$\sigma$	$M \pm \varepsilon(M)$	$\sigma$
Men					
Group I: extremely good	63	$16.30 \pm 0.52$	4.17	$20.28 \pm 0.45$	3.55
» II: good	60	$14.01 \pm 0.31$	2.38	$17.33 \pm 0.41$	3.14
» III: bad	51	$12.65 \pm 0.23$	1.66	$14.85 \pm 0.27$	1.95
» IV: extremely bad	55	$12.08 \pm 0.21$	1.56	$14.45 \pm 0.31$	2.27
Women					
Group I: extremely good	61	$17.08 \pm 0.31$	2.42	$22.25 \pm 0.47$	3.67
» II: good	76	$14.79 \pm 0.28$	2.40	$18.64 \pm 0.34$	2.95
» III: bad	50	$13.72 \pm 0.28$	1.96	$16.56 \pm 0.36$	2.57
» IV: extremely bad	50	$13.20 \pm 0.27$	1.93	$15.43 \pm 0.30$	2.11

*Mastication coefficient and number of chews.*

To see what significance there is in the fact that a person does not always chew the same number of times, a comparison has been made between persons who have chewed exactly 20 and 40 times respectively. First of all, we give in Table 53 the mean values for the mastication coefficients in such comparisons between adult men and women.

The figures in the table show that, as expected, the mastication coefficient in both 20 and 40 chews gets less as the set of teeth gets worse. (The differences between extremely good and good sets, and between good and bad sets, are significant both for men and for women, but for neither is this the case in regard to the difference between bad and extremely bad sets.) A comparison of the mastication effect between men and women shows that women possibly have higher values for the mastication coefficient, both in 20 and in 40 chews, although the differences are not significant, except for the groups of good sets and bad sets with 40 chews. Finally, the table shows that the variability decreases from good to bad sets of teeth to possibly a higher degree in men than in women.

TABLE 54.

Means of differences between mastication coefficients in tests with 20 chews and 40 chews respectively. Grown-up men and women, divided into groups with sets of teeth in different condition.  $n$  = number of persons.  $+$  means that the mastication coefficient in tests with 40 chews is greater than the mastication coefficient in tests with 20 chews.

Set of teeth	Men		Women	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
Group I: extremely good	63	$+ 3.98 \pm 0.54$	61	$+ 5.17 \pm 0.27$
> II: good	60	$+ 3.32 \pm 0.31$	76	$+ 3.86 \pm 0.21$
> III: bad	51	$+ 2.20 \pm 0.23$	50	$+ 2.84 \pm 0.23$
> IV: extremely bad	55	$+ 2.38 \pm 0.24$	50	$+ 2.23 \pm 0.22$

Meanwhile, it is of special interest that the masticatory effect considerably increases when the number of chews is raised from 20 to 40. The increase seems to be as large for men as for women. To investigate more closely the difference in masticatory effect between 20 and 40 chews, figures are given in Table 54 of differences calculated on the individual values for mastication coefficients (thus, they have not been obtained from the mastication coefficient means in the previous table).

We might now expect to get something approaching double the masticatory effect in the same teeth classes, on the increase of the number of chews from 20 to 40. Quite apart from the number of chews and the nature of the set of teeth (which in this case is not, of course, of any importance, as the comparison of the effect concerns the same individuals), other factors, already discussed, also influence the masticatory effect. It is therefore interesting to investigate, firstly, how great the increase is in the same teeth classes, and, secondly, whether the increase takes place to the same degree in the various sets of teeth. If we begin by comparing the differences in effect in variously good sets of teeth, we see from the figures in the table that the difference between the mastication coefficients in 40 and 20 chews grows less from extremely good to extremely bad sets. The differences between the classes are not significant throughout, however. (For men, there are probable differences between groups I and III, I and IV, and II and III. Women show significant differences between all groups except III and IV.) To gauge the increase of the mastication effect when the number of chews rises from 20 to 40, the

TABLE 55.

Mastication coefficients for grown-up men and women with extremely good or extremely bad sets of teeth, distributed with regard to number of chews.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.

Number of chews	Men		Women	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
Extremely good set of teeth				
Below the 1st quartile	16	$19.9 \pm 1.1$	16	$21.8 \pm 1.3$
Between the 1st quartile and the median	16	$22.2 \pm 1.3$	15	$24.0 \pm 1.3$
Between the median and the 3rd quartile	16	$26.1 \pm 1.4$	15	$25.5 \pm 1.3$
Above the 3rd quartile	15	$30.1 \pm 2.2$	15	$26.1 \pm 0.9$
Extremely bad set of teeth				
Below the 1st quartile	15	$13.92 \pm 0.50$	13	$14.88 \pm 0.33$
Between the 1st quartile and the median	12	$16.16 \pm 1.30$	12	$16.17 \pm 0.46$
Between the median and the 3rd quartile	15	$16.24 \pm 0.80$	12	$18.10 \pm 0.63$
Above the 3rd quartile	13	$16.99 \pm 0.85$	13	$19.51 \pm 0.73$

difference between the mastication coefficients for both 20 and 40 chews has been reckoned in per cent of the mastication coefficient value at 20 chews. We then find that for men, the increase in extremely good and good sets of teeth amounts to about 24 per cent, and in bad and extremely bad sets to about 20 per cent. The corresponding figures for women are rather more than 30 per cent, and not quite 17 per cent, respectively.

It would have been interesting to investigate the increase in masticatory effect with a higher number of chews, e. g. 80, and compare this effect with the values for the mastication coefficient in 20 and 40 chews. Such tests have not been made, since it was thought that yet another test would prove rather too much for the subjects. All the same, a comparison can be made by grouping the material according to number of chews into 4 equal groups, and comparing the masticatory effect in low and high numbers of chews.

Table 55 gives the means for mastication coefficients in extremely good and extremely bad sets of teeth for adult men and women. The material is grouped within limits, set with the help of medians and quartiles, for the number of chews. An increase is found which is admittedly not significant from the one group to the next, but which nevertheless persists throughout. If those with a high number of chews are compared with the

group showing a low number of chews, we find significant differences for both men and women, and in extremely good and bad sets of teeth alike. (In extremely good sets of teeth in women, however, the difference is only probable.) If the difference is, as before, expressed in per cent of the lower value for the mastication coefficient, we get more comparable figures, which seem larger for the men than for the women, in so far as men with extremely good sets of teeth have the highest per cent figure for the increase ( $51 \pm 12$  per cent), and women with extremely good sets the lowest one ( $19.7 \pm 7.3$  per cent). The inequality in the differences (which is not significant) is probably for the most part conditioned by chance, however, which, of course, transpires from the standard errors. In extremely bad sets of teeth, the corresponding figures for men are  $22.1 \pm 7.1$  per cent, and for women  $31.1 \pm 4.1$  per cent.

Of further interest now is to try and get an idea of the proportion of the changes in mastication coefficients, due to a changed number of chews. We must then get an approximate idea of the average number of chews characterizing these groups. By means of a special collocation, the mean number of chews has been calculated in each group. Thus, for men with extremely good sets of teeth, the average number for the first group is 40, for the second group 55, for the third group 74, and for the fourth group 107. Average coefficients corresponding to these values are 20, 22, 26, and 30 respectively. As has previously been shown, a mastication coefficient of 16 corresponds to 20 chews. This signifies that when the number of chews increases about 5 times, the mastication coefficient is only increased about 2 times. If we plot mastication coefficients against number of chews on a graph, we find that the changes in the mastication coefficient in relation to the number of chews follow a more or less straight line. The same investigation has been made on women with extremely good sets of teeth, and also for men and women with extremely bad sets. We find differences, which, however, probably lie within the limits for the standard error, and which imply a proportionately fainter increase of the mastication coefficient values in relation to the number of chews. All the same, the increase still follows a more or less straight line. Further, it is of special interest that, as pointed out above, the increase in the mastication coefficient is not proportionate to the increase in the number of chews.

To throw further light on the connection between masticatory



TABLE 56.

Correlation between mastication coefficients and number of chews. Grown-up men and women divided into groups with sets of teeth in varying condition.  $n$  = number of persons.  $r \pm \varepsilon(r)$  = correlation coefficient  $\pm$  standard error.

Set of teeth	Men		Women	
	$n$	$r \pm \varepsilon(r)$	$n$	$r \pm \varepsilon(r)$
Group I: extremely good	63	$+0.667 \pm 0.070$	61	$+0.330 \pm 0.114$
» II: good	60	$+0.588 \pm 0.084$	76	$+0.527 \pm 0.083$
» III: bad	51	$+0.550 \pm 0.098$	50	$+0.518 \pm 0.103$
» IV: extremely bad	55	$+0.294 \pm 0.122$	50	$+0.749 \pm 0.062$
Groups I—IV:	229	$+0.429 \pm 0.054$	237	$+0.346 \pm 0.057$

effectivity and the number of chews, correlations between the number of chews and the mastication coefficient have been calculated for adult men and women. Seeing that, as has been shown above, there is a practically straight-line connection, Bravais-Pearson's correlation coefficient has been used at the calculations. Table 56 gives the values for correlation coefficients for adult men and women with varying sets of teeth. From the figures in the table we can see that there is, both for men and for women, a definite correlation between the masticatory effectivity and the number of chews: for men  $r = +0.43 \pm 0.05$ , and for women  $r = +0.35 \pm 0.06$ . For the former, the correlation drops from 0.67 to 0.29, reckoning from extremely good to extremely bad sets of teeth, and for the latter, from  $+0.75$  to  $+0.33$ , reckoning from extremely bad to extremely good sets of teeth. The differences between neighbouring groups are not statistically significant, however, either for men or for women. On the other hand, the extreme groups show a significant difference for women, and a probable one for the men. If we compare the correlation between the two sexes, we find the values agreeing in good and bad sets of teeth. In the extreme groups, on the other hand, we find the correlation for women about half that for the men in extremely good sets of teeth, and about 2.5 times as large in extremely bad sets. The difference in the former case is probable ( $+0.34 \pm 0.13$ ), and in the latter case, significant ( $+0.45 \pm 0.14$ ).

Having now found a distinct correlation between mastication coefficient and number of chews, the correlation has been cal-

TABLE 57.

Correlation between number of chews in two successive tests. Grown-up men and women with extremely good or extremely bad sets of teeth.

$n$  = number of persons.  $r \pm \varepsilon(r)$  = correlation coefficient  $\pm$  standard error.

Set of teeth	Men		Women	
	$n$	$r \pm \varepsilon(r)$	$n$	$r \pm \varepsilon(r)$
Group I: extremely good	63	$+0.928 \pm 0.017$	61	$+0.940 \pm 0.015$
IV: extremely bad	55	$+0.734 \pm 0.062$	50	$+0.914 \pm 0.028$

culated for men and women in the extreme groups (extremely good and extremely bad sets of teeth) between the number of chews in two consecutive tests, where the portion was chewed until it felt ready to swallow. Figures are given in Table 57.

The figures in the table show the correlation between the number of chews in consecutive tests to be very strong. Here, there is excellent agreement between men and women with extremely good sets of teeth; extremely bad sets, however, show a probable difference between men and women. The strong correlation tallies with the fact, shown earlier on, that the variation in the number of chews is comparatively small between two tests coming one after the other.

Taking this fact into account, it has been interesting to investigate how strong a correlation in mastication effect is to be found in two consecutive tests. Figures are given in Table 58.

The figures show that, as expected, the correlation between mastication coefficients in extremely good and extremely bad sets of teeth is extremely high, for both men ( $r = 0.87 \pm 0.03$ ) and women ( $r = 0.71 \pm 0.06$ ). We also find, as we did from the values in Table 56, that the correlation seems, for men, to be higher in extremely good sets of teeth than in extremely bad ones, and for women, vice versa, though the differences are not significant, all the same. We also find that the correlation coefficient for men with extremely good teeth agrees with the value for women with extremely bad sets, and that the correlation coefficient for women with extremely good sets of teeth agrees with the value for men with extremely bad ones.

The high correlation coefficient values, which we have now found in calculating the correlation between the number of chews

TABLE 58.

Correlation between mastication coefficients in two successive tests. Grown-up men and women with extremely good or extremely bad sets of teeth.

$n$  = number of persons.  $r \pm \varepsilon(r)$  = correlation coefficient  $\pm$  standard error.

Set of teeth	Men		Women	
	$n$	$r \pm \varepsilon(r)$	$n$	$r \pm \varepsilon(r)$
Group I: extremely good	63	$+ 0.873 \pm 0.030$	61	$+ 0.716 \pm 0.063$
IV: extremely bad	54 <sup>1</sup>	$+ 0.704 \pm 0.069$	50	$+ 0.850 \pm 0.039$

and the mastication coefficient, show that the variation in the number of chews is a fundamental cause of the variation in the mastication effectivity.

*Mastication coefficient and the condition of the teeth.*

The variation in the masticatory effectivity is also connected with variation in the sets of teeth, which latter can now be numerically evaluated in two different ways with the methods worked out by the author. The correlation can be calculated between the point values of the teeth or the occlusion surface on the one side (as expressing the character of the set of teeth), and the computed mastication coefficients, on the other. The correlation coefficients thus obtained will then give an idea of the connection between the nature of the set of teeth and the masticatory effectivity.

Correlation calculations are in the first place made between the masticatory effectivity and the number of occlusion contacts. They show that there is a strong correlation between the mastication coefficient and the number of contacts. The values for the correlation coefficient show good agreement between men and women, amounting for the former to  $0.572 \pm 0.044$ , and for the latter to  $0.566 \pm 0.044$ . Corresponding calculations have also been made for men and women with regard to the connection between the mastication coefficient and the occlusion surface. This calculation, too, shows a strong correlation, with a coefficient of  $0.617 \pm 0.041$  for men, and of  $0.491 \pm 0.050$  for women. There are no significant

<sup>1</sup> Information is lacking for 1 case of 55.

differences between the correlation coefficients obtained from the calculated points, and those obtained from the occlusion surface. The investigation supports the notion that the nature of the set of teeth is quite as important to the masticatory effectivity as is the number of chews.

It has been mentioned earlier on that the investigated material of adult men and women contain isolated cases of malocclusion. All cases that came for investigation have been included, in order to get a representative material. The cases with malocclusion have been registered, so that it is possible to investigate their masticatory effectivity. For a rough orientation, the author has confined himself to tabulating the extent to which dental anomalies occur above and below the median for the mastication coefficients in the different groups. Of the total material of 466 adult men and women, we find 103 individuals with anomalies, i. e.  $22.1 \pm 1.9$  per cent. If the anomalies had been of no importance, we should have expected  $50.0 \pm 4.9$  to lie above the median for the respective groups, and the same number to lie below. The figures obtained are 39.8 per cent above the median, and 60.2 per cent below. There is no significant deviation from what we should expect from chance. It is possible that significant differences might be obtained from a larger material. All the same, the figures we get do not indicate that the cases of anomaly displayed a more divergent mastication effect than other individuals, and their values lie, for the rest, well within those of the normal range of variation.

### *The range of variation.*

Table 59 shows the distribution in both sexes for the whole of the lumped together material. Here, a class division of  $0.5 \sigma$  round the means has been used for men and women respectively. The distribution is somewhat skew, in so far as high extreme values appear more extensively than low extreme values. The distribution appears to go from  $2 \sigma$  below the mean (for men,  $19.01 \pm 0.59$  sq. em./e. em., and for women,  $20.23 \pm 0.32$  sq. em./e. em.), up to  $4 \sigma$  above the mean (cf. Table 59). It is, however, worthy of note that one man had a mastication coefficient that deviated more than  $5 \sigma$  from the mean: it was  $49.6$  sq. em./e. em. This person was, on principle, an eater of raw vegetables, and chewed extremely thoroughly, reaching 142 times. Thus he exhibited an

TABLE 59.

Distribution of mastication coefficients and occlusion surfaces. Total material of grown-up men and women. As class interval has been used for men:  $0.5\sigma = 2.9$  sq. cm./c. cm. and  $= 62.9$  sq. mm.; for women:  $0.5\sigma = 2.4$  sq. cm./c. cm. and  $= 55.7$  sq. mm.  $M = \text{mean}$ .

Class intervals	Men				Women			
	Mastication coefficient		Occlusion surface		Mastication coefficient		Occlusion surface	
	Number	%	Number	%	Number	%	Number	%
4 $\sigma$	—	—	—	—	1	0.4	—	—
3.5 $\sigma$	3	1.3	1	0.4	—	—	—	—
3 $\sigma$	2	0.9	2	0.9	4	1.7	1	0.4
2.5 $\sigma$	3	1.3	2	0.9	4	1.7	3	1.3
2 $\sigma$	10	4.4	10	4.4	9	3.8	11	4.8
1.5 $\sigma$	11	4.8	22	9.7	20	8.4	24	10.4
1 $\sigma$	27	11.8	36	15.9	28	11.8	36	15.6
$^+M$ 0.5 $\sigma$	34	14.8	41	18.1	45	19.0	41	17.7
— 0.5 $\sigma$	54	23.7	35	15.4	40	16.9	42	18.1
1 $\sigma$	63	27.5	43	18.9	47	19.8	32	13.9
1.5 $\sigma$	20	8.7	19	8.4	35	14.8	23	10.0
2 $\sigma$	1	0.4	13	5.7	4	1.7	13	5.6
2.5 $\sigma$	—	—	3	1.3	—	—	5	2.2
Total	229 <sup>1</sup>	100.0	227 <sup>2</sup>	100.0	237	100.0	231 <sup>3</sup>	100.0

extreme value as regards number of chews, also. He belonged, incidentally, to the class with extremely good teeth.

It has been mentioned earlier that the number of chews, too, shows a skew distribution, extending from 2  $\sigma$  inclusive, up to almost 3.5  $\sigma$  round a mean of 67.8 chews for men, and 58.5 for women (cf. Table 46). It is interesting to investigate the distribution with regard to occlusion surface, also. Figures for this are included in Table 59, where it is seen that the occlusion surface varies from 2.5  $\sigma$  below the mean up to 3—3.5  $\sigma$  above the mean, which is  $299.7 \pm 8.3$  sq. mm. for men, and  $295.1 \pm 7.3$  sq. mm. for women. Here, too, then we have a skew distribution. Actually, the skew distribution of the mastication effect is probably connected with the asymmetry which is found both for the number of chews and the occlusion surface.

<sup>1</sup> With regard to mastication coefficient there is one of 229 individuals between  $+5\sigma$  and  $+5.5\sigma$ , corresponding to 0.4 per cent of the material.

<sup>2</sup> Information is lacking for 2 of 229 persons.

<sup>3</sup> " " " " 6 of 237 "

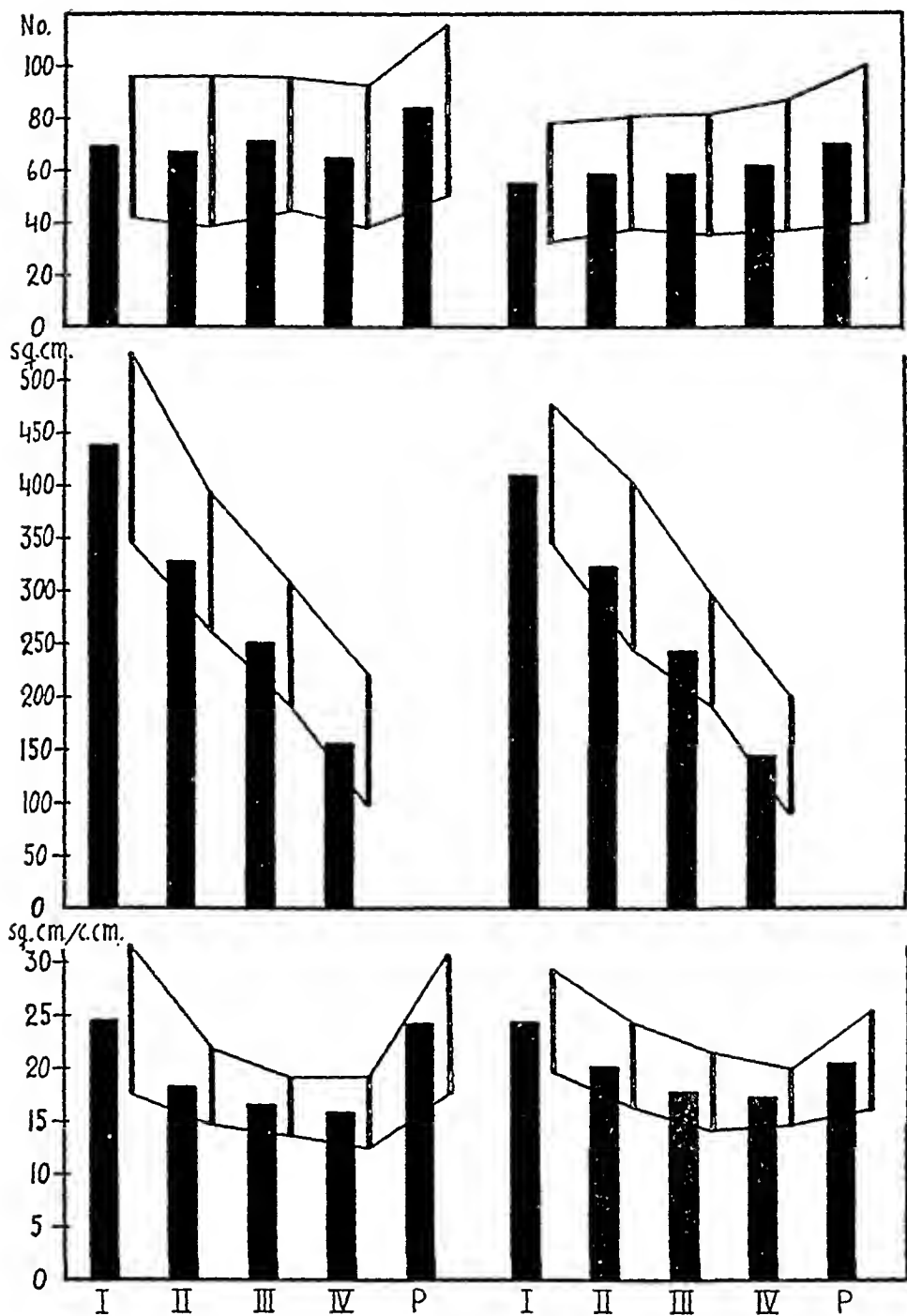


Fig. 7. At the top, the number of chews, on the second line, the occlusion surface, at the bottom, mastication coefficients, for men (to the left) and women (to the right) with different sets of teeth (groups I—IV) and with prostheses (P). The black columns give the means and the vertical lines the standard deviation.

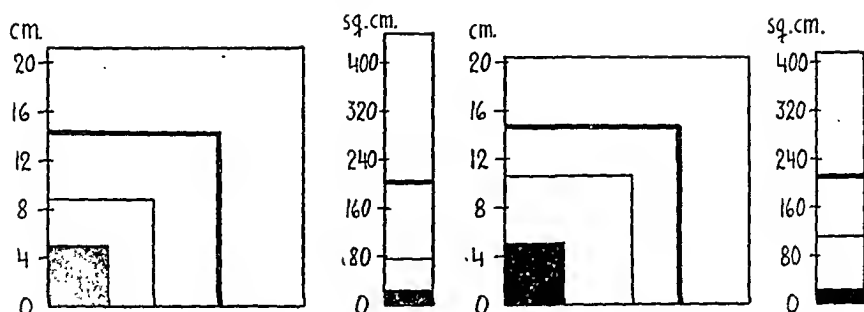


Fig. 8. Diagram showing the surface of the test after chewing, in comparison with the surface of the test portion. To the left men, to the right women. For both are given two diagrams, one with the surface expressed in squares and another with the surface expressed in the height of a column. The surface of the test portion is black, the mean after chewing is given in thick lines, the limits for the range of variation in thin lines.

Finally, Figure 7 shows both mean and range of variation for the number of chews, the occlusion surface, and the mastication coefficient, for adult men and women. We can see from the diagram that, as has been shown earlier on, the average number of chews and its variability remain constant when the set of teeth gets worse; we also see that the average occlusion surface decreases strongly and in a straight line in the different classes. The differences towards a smaller standard deviation which occur are not of importance. Then Figure 7 shows that the masticatory effectivity diminishes — though much less markedly than the occlusion surface — for the different classes, at the same time as the standard deviation also diminishes somewhat. The diagram is intended to summarize the results obtained earlier.

To elucidate the mastication coefficient and its range of variation a survey is given in Figure 8 of the average surface enlargement found in adult men and women in relation to the original surface of the test portion. The diagram also gives the limits for the range of variation. The figure refers to the lumped together material of men and women with sets of teeth of varying types.

#### *Individual and interindividual variation.*

To get a more differentiated idea of the general variation in the mastication effect, we now divide up the variation for adult men and women into the individual variation which conditions

TABLE 60.

Total standard deviation of the mastication coefficient ( $\sigma_t$ ) for men and women, divided into groups with different sets of teeth, individual standard deviation ( $\sigma_i$ ) and calculated inter-individual standard deviation ( $\sigma_p$ ) for the corresponding groups.  $n$  = number of persons.

Set of teeth	$n$	$\sigma_t$	$\sigma_i$	$\sigma_i$ in % of $\sigma_t$	$\sigma_p$	$\sigma_p$ in % of $\sigma_t$
Men						
Group I	63	7.04	2.54	36.1	6.57	93.3
" II	60	3.65	1.82	49.9	3.16	86.6
" III	51	2.79	1.46	52.3	2.30	82.4
" IV	55	3.31	1.68	50.8	2.85	86.1
Groups I—IV	229	5.82	1.96	33.7	5.48	94.2
Women						
Group I	61	4.79	2.54	53.0	4.06	84.8
" II	76	4.02	1.68	41.8	3.65	90.8
" III	50	3.74	1.05	28.1	3.59	96.0
" IV	50	2.62	1.01	38.5	2.42	92.4
Groups I—IV	237	4.80	1.74	36.3	4.47	93.1

differences between repeated tests of one and the same person, and the variation which is found between different persons after the individual variability has been subtracted from the total one (cf. Chapter 12). Figures obtained in this way are given in Table 60. The table gives, then, for adult men and women with different sets of teeth, firstly the observed total variability,  $\sigma_t$ , secondly the individual variability,  $\sigma_i$ , thirdly the calculated interindividual variability,  $\sigma_p$ . We have discussed before the variability for different teeth groups, and shown that it drops from extremely good to extremely bad sets both in men and women. The individual variability shows a similar drop, as does also the interindividual variability. This means that if we calculate the respective sizes of the individual variability and the interindividual variability in per cent of the total variability, we get figures that remain fairly constant. The variations that do occur are probably, at any rate in large measure, due to chance. On the whole, the interindividual variability is 90 per cent of the total, and the individual variability 40—50 per cent of the total. The figures do not, of course, add up to 100 per cent.



If, lastly, we look at the lumped together material, we find the interindividual variability taking the rather larger share in the total variability of not quite 95 per cent, while the individual variability is about 35 per cent. In this material, the interindividual variability will, of course, form a larger proportion, as the lumping together of different classes of teeth is a further reason for variability in the form of an increased variation in the occlusion surface.

The fact that we get a varying result — i. e. an individual variability — when one person carries out repeated tests, is due to his chewing a different number of times, but it is certainly also due to the chews being, in other ways too, carried out differently. In consideration of the fact that the chewing habits, as has been shown earlier on, are comparatively constant, it is probable that these other factors play a not unimportant part.

The far greater variability in respect of differences between individuals is conditioned both by a great variability in the number of chews, and also by a greater variability in the occlusal surface. In the light of the correlation coefficients computed earlier, we have most reason to suppose that these two factors are of about equal importance. But here, too, we have to reckon with different degrees of skill in the management of the mouthful, the fact that some people chew harder than others, and dissimilarities in the anatomical structure of the set of teeth, which cannot be measured by the occlusion surface with the method used here.

## Mastication effect with full prosthesis.

In a population, there are, of course, a not inconsiderable number of persons, mainly the rather older ones, who have no teeth of their own, and who must resort for chewing food to artificial teeth. It is of interest from a practical viewpoint to try and get an idea of the mastication effect in chewing with full prosthesis, and it is also interesting to see how effective the masticatory powers in persons with full prostheses are, compared with persons who have their own teeth.

In describing the material in Chapter 8, we gave figures in Table 13 of the age and sex of the investigated persons with full prostheses. We will only mention here that these persons consisted of 50 men and 50 women between about 40 and 80 years of age, most of them between 55 and 70. The prostheses were grouped into three groups: extremely good, good, and bad. The motives for grouping were subjective, building on an estimation of the stability and suction powers of the dentures, and also on the occlusion of the rows of teeth. When grouping, the author confirmed his judgments by asking the wearers how good they themselves thought their dentures were, for chewing. As a rule, their assessments seem to have agreed with his.

The first concern here was to get an idea of the masticatory effectivity in full prostheses of a fairly ordinary nature, where their owners had become used to them. In other words, the investigation concerns full prostheses that have been in use some time. The author's general impression of the prostheses investigated was that they were not of a very superior order, but not (with a few exceptions) below standard, either. It may be mentioned that a number of them were made at dental clinics, treating those who cannot afford to pay.

It is a generally accepted view that it is difficult to chew with full dentures. A reason for this given in the literature, for example, is that one cannot chew so hard as with one's own

teeth, so that it is difficult to crush the food between the tooth surface. In addition to this, the prostheses, in particular the lower ones, are often considered difficult to manage in chewing.

The question now is, whether these factors really do impair the powers of mastication. After all, the food we consume consists mainly of soft substances, which should not be difficult for the wearer of dentures to chew. On the other hand, firm, firm and brittle, and tough substances perhaps are hard for them to chew. The patient was asked to say which substances gave him trouble. The opinions given here agreed, on the whole, with one another, being briefly as follows. Of the soft foodstuffs, such as were of an adhesive nature, e. g. soft bread, pancakes and the like, were considered hard to chew. The trouble here was that the under jaw sticks in the mouthful and may then easily get out of position. Firm, and firm and brittle substances were not considered troublesome, on the other hand. On the contrary, it was generally maintained that hard bread was easy to chew, and far preferable to soft bread. Nor did the test subjects find raw earrot, fresh fruit etc. difficult, provided the mouthful was not very large. Tough meat was considered troublesome. A number of test subjects said that meat could be chewed: others said that they ate meat cut up into small pieces and swallowed without any real chewing previously.

The general impression the author got from these questions was that adhesive and tough food substances cause trouble in chewing, while soft, firm, and firm and brittle substances are comparatively easy to cope with.

### *Prosthesis and number of chews.*

When the specimens were taken, the number of chews was counted in the same way as before. Table 61 gives average values for the number of chews taken by men and women with extremely good, good and bad prostheses in chewing the portion until it felt ready to swallow. The figures in the table show that the number of chews increases from extremely good to bad prostheses, both in men and women. The difference between the number of chews with extremely good and with bad prostheses is just about probable for men ( $27.0 \pm 11.0$ ). A comparison between the mean number of chews for men and for women shows that, on an average, the men chew a greater number of times. The greatest difference between

TABLE 61.

Number of chews in men and women with full prostheses of varying quality.  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.  $V$  = variation coefficient.

Prosthesis	Men				Women			
	$n$	$M \pm \varepsilon(M)$	$\sigma$	$V$	$n$	$M \pm \varepsilon(M)$	$\sigma$	$V$
Extremely good	17	$67.1 \pm 5.7$	23.7	35.4	8	56.8	—	—
Good	19	$88.8 \pm 4.3$	18.5	20.9	22	$67.4 \pm 5.2$	24.3	36.1
Bad	14	$94.1 \pm 9.5$	35.5	37.7	20	$78.0 \pm 3.7$	16.4	21.0
Total	50	$82.9 \pm 3.9$	27.7	33.3	50	$69.9 \pm 3.0$	21.1	30.2

the two sexes is found in chewing with moderately good prostheses. This difference is significant ( $21.4 \pm 6.7$ ). The figures, then, show men with prostheses to have chewed more than women, and also show that men with bad prostheses chew a greater number of times than men with extremely good ones. As the number of investigated women with extremely good prostheses is very small, we cannot see from the figures whether there is a difference there between the number of chews with extremely good and with bad prostheses, though the great difference between the means rather indicates that there is.

A comparison can now be made between the average number of chews for adult men and women with their own teeth, on the one hand (cf. Table 40 and 41), and for men and women with full dentures on the other. In *men*, the values for extremely good dentures agree with those for extremely good sets of teeth. Persons with good full dentures chew, on an average, a larger number of times than adult men with their own teeth. The difference in chews between good sets of teeth on the one side, and good dentures on the other, is statistically significant ( $21.9 \pm 5.7$ ). (The figures for the number of chews with bad dentures is high, but has at the same time a high standard error, and give no significant difference between bad sets of teeth and bad dentures.) A comparison of the number of chews between *women* with their own teeth and women with full dentures shows in the same way as for men, tallying values for extremely good sets of teeth and extremely good dentures. The number of chews in good and bad dentures is higher than in good and bad sets of teeth, with a significant difference between bad sets of teeth and bad dentures of  $19.4 \pm 4.9$ . These compa-

risons indicate that persons with good dentures do not, on an average, chew more times than persons with their own teeth, whereas persons with good and bad dentures do.

*Prosthesis and mastication coefficient.*

This difference in the number of chews may, as far as the masticatory effect is concerned, compensate the lower effectivity of bad dentures, so that there is no noticeable difference in the comparison of mastication coefficients between good and bad dentures. There is therefore reason to compare the mastication effect in good and in poor prostheses when the number of chews is constant, i. e. 40. Figures are given in Table 62.

We find for men that there is a statistically significant difference in mastication coefficient between extremely good and bad dentures (difference  $7.2 \pm 1.5$ ), and also between extremely good and good dentures ( $5.5 \pm 1.4$ ). On the other hand, the difference between good and bad dentures is not significant; this may be due to elements of uncertainty in classifying. There is, however, a probable difference ( $2.11 \pm 0.82$ ) for women between these groups of dentures.

It now remains to compare the mastication effect between persons with full dentures and persons with their own teeth. If we compare the different groups of dentures, we find no statistically significant or probable differences between the groups in unrestricted chewing; this implies that people with bad prostheses compensate the lowered effectivity by chewing a larger number of times. In itself, this is, perhaps, not so astonishing. We can suppose that a person who has been given false teeth will chew under such altered circumstances as to cause him to break his earlier habits. In developing new ones, he pays a certain attention to the mastication effect. All the same, it is possible that the increased number of chews does not entirely level out the differences, in so far as we find a difference of  $6.0 \pm 2.5$  for the average mastication coefficients between the groups of good and bad dentures in men. It is possible, that is to say, that we should get a significant difference on a larger material. Since, in each group, the number of persons with full dentures is small, we get better criteria if we compare the mastication coefficients for the total number of men and women respectively.

TABLE 62.

Mastication coefficients in tests with 40 chews for men and women, divided into groups with prostheses of varying quality.  $n$  = number of persons.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

$V$  = variation coefficient.

Prosthesis	Men				Women			
	$n$	$M \pm \varepsilon(M)$	$\sigma$	$V$	$n$	$M \pm \varepsilon(M)$	$\sigma$	$V$
Extremely good	17	$22.74 \pm 1.14$	4.68	20.6	8	17.48	—	—
Good	19	$17.29 \pm 0.88$	3.83	22.1	22	$17.61 \pm 0.66$	3.09	17.5
Bad	14	$15.58 \pm 0.91$	3.39	21.8	20	$15.50 \pm 0.48$	2.15	13.9
Total	50	$18.66 \pm 0.70$	4.93	26.4	50	$16.74 \pm 0.40$	2.86	17.1

If, then, we lump together the entire material, we find for men a mastication coefficient of  $24.08 \pm 0.91$ , and a standard deviation of  $6.65 \pm 0.66$ . The variation coefficient is  $27.6 \pm 2.76$  per cent. For women, the mean is  $20.17 \pm 0.63$ , the standard deviation  $4.41 \pm 0.14$ , and the variation coefficient  $21.7 \pm 2.17$  per cent. There is a small significant difference between men and women with dentures, possibly partly connected up with the fact that women with dentures chew a lesser number of times than men with dentures (difference  $3.61 \pm 1.13$ ). It must be remembered, however, that the average age of the women is higher than the average age for the men.

The main interest centres round a comparison with the figures for adult men and women with their own teeth (cf. Table 49). We find that persons with full dentures have a mastication effect which is not significantly different from that in men with extremely good teeth, but which is perhaps somewhat lower. The same is true of women. It is interesting to be able to ascertain that prosthesis gives, on an average, about as good a result as an extremely good or good set of teeth when chewing a substance which, though not representing in consistency the food which is most troublesome to chew, nevertheless borders on the upper limit of difficulty for normal food. The results obtained here agree with the details given by the patients themselves, which have been described earlier on. Full prosthesis gives, as a rule, a satisfactory or even good mastication effect.

It is finally of interest to discuss, in this connection, the variability in mastication effect. We have shown earlier on that

TABLE 63.

Number of individuals ( $=n$ ) in groups with sets of teeth in varying condition, distributed according as the mastication coefficient is greater or smaller than the average mastication coefficient for the total number of examined men and women respectively, and average number of chews ( $M_n$ ) in the groups in question.  $N$  = total number of persons.  $M$  = mean.

Set of teeth	$N$	Above $M$			Below $M$		
		$n$	$n$ in % of $N$	$M_n$	$n$	$n$ in % of $N$	$M_n$
Men							
Group I: extremely good	63	50	79.4	72.1	13	20.6	55.2
» II: good	60	23	38.3	83.0	37	61.7	56.9
» III: bad	51	10	19.6	89.2	41	80.4	66.2
» IV: extremely bad	55	8	14.5	76.5	47	85.5	63.3
Women							
Group I: extremely good	61	52	85.2	67.2	9	14.8	41.0
» II: good	76	40	52.6	77.2	36	47.4	49.1
» III: bad	50	13	26.0	76.1	37	74.0	63.8
» IV: extremely bad	50	6	12.0	100.5	44	88.0	73.8

sets of teeth can also chew as effectively, or better, than the average in a population of adult men and women.

It is, perhaps, more interesting to try and get an idea of how far the chewing of persons with varying sets of teeth is above the average for persons with extremely bad teeth (cf. Table 64). Here, too, we find considerably higher figures for extremely good sets of teeth than for extremely bad ones. About half of those with extremely bad sets are above the group mean, which is, of course to be expected. A more important fact is, that among persons with extremely good sets of teeth, 7—8 per cent chew worse than the average mastication for persons with bad sets. In other words, the low mastication effect in these former is not due to lack of teeth. If they wish to make the effort, they can of course achieve a very good effect. Their chewing habits are such, however, that they content themselves with a poor effect.

It has been said earlier on that, when we are to investigate the mastication effect in separate individuals with the help of the test tried out here, we get an uncertain value from a single test, but that a series of tests should lead to a fairly exact impression. In most cases, about ten tests should be enough, which implies that we have to reckon with a standard error of about 3

TABLE 64.

Number of individuals ( $=n$ ) in groups with sets of teeth in varying condition, distributed according as the mastication coefficient is greater or smaller respectively than the average mastication coefficient for the group with extremely bad sets of teeth (men and women), and average number of chews ( $M_n$ ) in the groups in question.  $N$  = total number of persons.  $M$  = mean.

Set of teeth	$N$	Above $M$			Below $M$		
		$n$	$n$ in % of $N$	$M_n$	$n$	$n$ in % of $N$	$M_n$
Men							
Group I: extremely good	63	58	92.1	70.1	5	7.9	51.2
» II: good	60	45	75.0	72.9	15	25.0	48.7
» III: bad	51	28	54.9	82.5	23	45.1	56.4
» IV: extremely bad	55	23	41.8	77.0	32	58.2	56.8
Women							
Group I: extremely good	60	56	93.3	57.7	4	6.7	32.3
» II: good	76	56	73.7	64.6	20	26.3	42.6
» III: bad	50	24	48.0	66.3	26	52.0	51.4
» IV: extremely bad	50	22	44.0	77.3	28	56.0	50.0

per cent. When this has given us an idea of how effectively the test subject chews with the set of teeth he has, we can fit him into the scale of varying mastication coefficients characterizing a normal population. If the test subject has a low mastication coefficient, there is reason to discuss prosthesis. The nearer he is to the lower limit for normal effectivity, the greater, of course, is the call for prosthesis from the point of view of effective chewing; greatest of all is it if he is below the value denoting the average for extremely bad sets of teeth, namely 15.77 sq. cm./c. cm. for men and 17.16 sq. cm./c. cm. for women. For purposes of comparison, it may be mentioned that  $8 \pm 3.8$  per cent of the men with full dentures, and  $18 \pm 5.4$  per cent of the women, have lower mastication coefficients than the average for men and women respectively with extremely bad teeth.

But we cannot, of course, judge the situation solely with regard to the mastication coefficient. We should also observe the chewing habits of the test subject, i. e. his average number of chews. It is therefore desirable, when testing a patient, to register the number of chews, and get a mean from them. If the figure is low, this naturally indicates that he is content with a comparati-



vely ineffectieve chewing. Even with an extremely good set of teeth, he would have had a comparatively low mastication effectivity. In consideration of this, we can, naturally, tolerate a lower mastication coefficient in a person like this than in a person with a large average number of chews.

Finally, let it be *firmly* laid down that the indications for prosthesis do not only consist of a poor mastication effect and a low mastication coefficient. Regard must also be paid to the nature of the set of teeth, and to the risk of faulty positions and alterations of different kinds being set up if prosthetic replacement is not made. This side of the matter is outside the scope of this work, however. All the same, an all-round estimation of the need of dentures should get a certain guidance from the results of an investigation with mastication test. From a practical point of view, we may lastly stress, in this connection, the importance of the way in which the dentures are made, and how the subjects can learn to use them. The points of view now put forward concern full dentures. Thus, the conclusions cannot be applied to partial dentures of various kinds. To judge these, special investigations are of course necessary.

For the sake of safety, we may once again remind readers that the conclusions drawn refer only to the test material which the author has used, and to food which has a corresponding consistency. Obviously, entirely different results are to be expected in chewing substances which are easier to reduce, as also in chewing substances with a more resistant consistency. Of course the size of the test portion is also of a certain importance. In other words, this investigation should be followed up with research into such questions.

## Summary.

The survey of the literature shows that little attention has been paid to the question of the physiological effect of the teeth in normal and in more or less defective sets. A few investigations have been carried out with straining of chewed test portions. The materials (almond, cocoanut) used in the tests were of a not very satisfactory nature. The methods used were uncertain, and did not succeed in giving any more definite idea of the mastication effect under different circumstances. Larger materials, and more representative ones, have not been investigated at all. It has therefore been necessary in the first place to work out a satisfactory *method for testing*.

1. After testing different materials, the one chosen was 15 per cent gelatin to which had been added 5 per cent barium sulphate and a red colouring-matter. From this cylindrical rods are cast, which are cut in a special apparatus (cf. Figure 1) into pieces with a volume of 10.6 c. cm. (7.4 c. cm. for children). The pieces are hardened in formalin, so that they do not dissolve in water. The formalin is subsequently removed by washing. The test material should answer reasonable demands in so far as it can be chewed even by people with poor teeth, without, however, being unduly easy to reduce to small pieces. Its consistency most nearly corresponds to that of raw carrot or boiled liver. The test material has been submitted to special tests to ascertain its compressibility and to establish the breaking-point in loading, and has proved to have a homogeneous character. A special apparatus has been constructed to carry out such tests (cf. Figure 2).

2. After the test portion has been chewed, the reduction is determined by straining through an apparatus (cf. Figure 3) consisting of a thick tube, with 10 strainers with the diameter of the holes going from 10 to 1 mm., there being 1 mm.'s difference between each. A rotating stream of water plays on the portion. The direction of the rotations is reversed after 48 seconds, with

pauses of 12 seconds. The water pressure is 1 metre. The straining of one test portion takes 6 minutes.

3. When establishing the degree of reduction, the first thing is to count the particles in the first 7 strainers. The number of particles in the last 3 are determined by sedimentation in graduated glass tubes when the particles are shaken down by a mechanical device. A special investigation has determined the number of particles per c. cm. of sedimented volume.

4. To get a uniform expression for the degree of reduction, a calculation is made of the total area of the particles composing the test portion after it has been chewed. In so doing, it is assumed that the particles on the first 7 fractions have, on an average, the form of cubes, whose sides have an average diameter lying between the holes in the strainer where the particle landed up, and the one immediately above. In the last 3 fractions, the particles are assumed to have, on an average, the shape of octahedrons, with diameters as the cubes. By means of a special investigation, it has been established that it is possible on these assumptions, to calculate with sufficient exactitude the volume of the test portion from the number of particles. The calculated volume diverges from the actual one with a standard deviation of about 10 per cent.

The calculated surface area has been checked by staining the portion with Congo-red, which is absorbed by the surface of the particles. After washing with water, the colour is dissolved with a certain quantity of 96 per cent alcohol, and the colour content determined colorimetrically. Colouration and decolouration of this kind, carried out on slices of gelatin with a known area, have given coefficients for the reckoning of the colorimetric values in sq. cm. of surface. The values thus obtained have agreed fairly well with those for the geometrically calculated surface for a series of 16 portions.

5. The values obtained for volume and surface area have been used to compute a *mastication coefficient* which gives sq. cm. of area per c. cm. of volume in the test portion. It is difficult to get a general survey of the size of the different fractions. The coefficient, however, gives a simple expression for the portion's degree of reduction. The coefficient is probably closely connected with what, from a physiological point of view, one wants to measure. The reduction of the test portion is, of course, of

importance, because mastication extends the surface so that the digestive juices have better play in the process of digestion. By double determinations of the mastication coefficient in a series of portions, the error of measurement has been established at 2.1 per cent, which can be considered small in view of the variability found when one person chews the test material in repeated tests. The individual variability in chewing nevertheless makes it necessary, when establishing the masticatory effectivity of a single person, to have him carry out a small number of tests, e. g. about 10, to get a reliable mean value. (The standard error for a mean of 10 tests should be about 3 per cent.)

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Using the methods worked out, *investigations have been made on a series of persons* of different ages and sex, and with more or less defective sets of teeth, and also on persons with full dentures; this was to get material for a closer analysis of the masticatory effectivity. The investigated material consists of 917 persons, distributed as follows: 100 7-year-old boys and girls, 100 13-year-old boys and girls (schoolchildren from Stockholm), 229 grown-up men (called up for military service), 237 grown-up women (female factory hands in Stockholm) — both groups 20—45 years of age — 101 older men and 50 older women of 50—75 years of age (selected material), and 50 men and 50 women of about 40—80 years of age (the majority between 55 and 70) with full dentures.

6. A special statistical treatment has been carried out as to the nature of the teeth, in order to characterize the material from a functional point of view. The statistical analysis has been made more thoroughly for the groups which can be considered as fairly representative for their respective layer of society. The set of teeth has been judged both with regard to its number of teeth, and with regard to teeth in occlusion, when (for grinders) the occlusal surface was gauged with the help of a wax impression, or the teeth were assessed according to a point scale. A special investigation has shown there to be a high correlation between the results of these two methods.

a) 7-year-old children, who have a maximum of 24 teeth, have proved throughout to have good ones. Front teeth are missing in 14.9 per cent, and grinders in 28.6 per cent.

b) 13-year-old children, who have a maximum of 28 teeth, have also good teeth. Front teeth are missing in 2.1 per cent, grinders in 8.8 per cent.

c) Grown-up men show a great variation. In the total material, however, incisors are missing only in 1.8 per cent, and grinders in 31.9 per cent.

d) For grown-up women, the corresponding figures are 1.4 per cent and 34.9 per cent. The agreement between men and women is good.

A particularly interesting fact is that, in grown-up men, wisdom teeth are found in 43.3 per cent, and in grown-up women only in 28.1 per cent. It may be mentioned that in a representative material of old men, the wisdom teeth have to a certain extent either not erupted or else have been destroyed early, but that they nevertheless are kept to a ripe old age in an unexpectedly large number, i. e. about 20 per cent. Because of the difficulties of diagnosing wisdom teeth, these figures, however, are not quite dependable.

To characterize the sets of teeth, a *contact coefficient* has been calculated which shows how many teeth correspond on the average to one contact in the table of points used by the author. The sets have further been grouped into four, according to the number of occlusion contacts. The limits have been set at quartiles and median in adult men and women, and this division has proved practicable throughout. (Among 13-year-olds group I, which comprises extremely good sets of teeth, has been split into two.) For grown-up men, for example, the contact coefficient for extremely good sets of teeth is 0.93 teeth, for good sets 1.20, for bad sets 1.36, and for extremely bad sets 1.78. As regards the details for the character of the sets of teeth, see Chapter 11.

7. Using the tried-out method, tests have been made registering the number of chews taken when the subject was allowed to chew until he considered the portion ready to swallow. Special tests have checked that the number of experimental chews agrees with the number taken when the portion is swallowed. It has been found that there are only small differences in the number of chews between grown-up men and women. The average number of chews is  $67.0 \pm 1.3$  for men, and  $58.4 \pm 1.1$  for women. Between groups with variously good sets of teeth there are no significant differences. This means that a poor set of teeth is not com-

pensated by a greater number of chews. There are also no differences either between older men and women and younger ones or as compared with 13-year-olds (if the different sizes of the test portions are taken into account). On the other hand, 7-year-olds seem to take a somewhat lower number of chews than the other groups. Here, the mean is  $49.7 \pm 1.1$ . It has further been possible to show that one person admittedly chews a somewhat varying number of times in repeated tests, but that this variability is not very large, consisting of 16.9 per cent for men and 13.3 per cent for women; this means that different individuals have different chewing habits: and that these habits as regards to the test used are quite firm, and fairly independent of the chewing result attained. Special investigations have also been carried out with different materials. They have shown, however, that material which is very troublesome to chew, such as indiarubber, increases the number of chews, while on the other hand, it gets lower for very easily chewed material, such as hard-boiled white of hen's egg.

8. Mastication coefficients have been used to investigate results when tests were made on persons with varyingly good sets of teeth, i. e. with different occlusal surface. Differences in the masticatory effectivity run parallel with deterioration in the sets of teeth. This may be expressed by saying that in grown-up men and women the surface of the original test portion is enlarged 11 times in extremely good sets of teeth, 8 times in good sets, 7 times in bad sets and 6.8 times in extremely bad sets. Nevertheless, the decrease in the mastication coefficient for grown-up men from, say,  $24.48 \pm 0.89$  sq. cm./e. cm. in extremely good sets of teeth to  $15.77 \pm 0.15$  sq. cm./e. cm. in extremely bad sets, is comparatively small compared with the decrease found as regards the occlusion surface. In grown-up men, the mastication coefficient drops by 35.6 per cent from good to extremely bad sets of teeth, while at the same time the occlusion surface drops by 64.3 per cent. For women, the corresponding figures are 29.5 per cent and 64.8 per cent. This means that though the effect of the teeth in a deteriorated set is *not* compensated by increasing the number of chews, it is, to a certain extent, by an increased skill in the management of the mouthful (when use of the incisors probably plays a part). Similar states of affairs have been seen in grown-up women, as also in old people and children. For the rest, there are slight differences between these groups. In a comparison between children and

adults no differences of importance were found. (A special investigation has been made into the influence of the different size of the test portions for adults and for children. It has been found that the difference is compensated by an increased chewing and therefore, figures for the mastication coefficients can be compared.) Older men chew somewhat more effectively in corresponding groups of teeth, which may be due to the teeth being abraded, thereby setting up better contacts between the teeth.

9. An investigation of the variability in the mastication effect has shown this to be relatively large, amounting to 20—30 per cent in groups with fairly similar sets of teeth. This must to a certain extent be due to the varying number of chews, and it has been possible to show that there is a distinct correlation between the number of chews and the mastication coefficient. For adult men, the correlation coefficient is  $+0.13 \pm 0.03$ , for women,  $+0.35 \pm 0.06$ . The importance of the number of chews has further been directly shown by comparative tests, when the subjects were made to chew 20 and 40 times respectively. The doubled number meant an increase in the effect by 20—30 per cent. All the same, the varying effect, too, must be connected with variations in the character of the sets of teeth. The correlation between the occlusion surface and the mastication coefficient is of the same order of magnitude as the above-mentioned correlation with the number of chews. It amounts to  $+0.62 \pm 0.01$  for the whole group of grown-up men, and to  $+0.19 \pm 0.03$  for the whole group of grown-up women. In other words, different chewing habits and differences in the sets of teeth seem to play about an equal part for the variation in the masticatory effect found in a population. Differences in skill and in the anatomy of teeth and jaws and other factors must also be of importance for the range of variation.

Finally, it has been shown that the individual differences in repeated tests give a comparatively moderate variability. For adult men and women alike, it amounts to 35 per cent of the total variability. This individual variation is connected with the fact that the number of chews made in the test varies in one and the same person. The number of chews in a population of adults varies from about 12 to about 165. The mastication coefficient varies from 7 sq. cm./e. cm. to 40 sq. cm./e. cm. for men, and from 10 sq. cm./e. cm. to 40 sq. cm./e. cm. for women. The distribution is

moderately skew as regards both the number of chews and the masticatory effect. Cf. Figs. 7 and 8.

10. A test of the chewing conditions with full dentures has shown that the average number of chews in persons with poor dentures is somewhat higher than that for persons with their own teeth. But there is no difference for good dentures. The effect, measured in mastication coefficient, corresponds on an average to that in extremely good or good teeth. Nevertheless, the variability is great. The prostheses have been classified as extremely good, good and bad; in so doing, regard was paid both to the way they are made and also to other circumstances giving reason to expect some to function better than others. Distinct differences in mastication effect have been found between these groups. At its best, a prosthesis gives a mastication effect as good as in persons with extremely good teeth of their own; at its worst, the effect is below the average obtained in persons with extremely bad teeth. Both when judging the need of dentures and when contemplating the advantages a certain prosthesis offers, the suggested test should prove of use, though in that case it is necessary to repeat it a number of times, e. g. about 10.



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AN EPIDEMIOLOGICAL AND CLINICAL STUDY

BY

*ROLF HALLGREN*

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DIRECTOR: DOCTOR C. W. LUNDQVIST

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MED. LIC., M.D.  
MEDICAL OFFICER OF HEALTH.

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*CONRAD BRUNKMAN*





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## Survey of literature.

The task of reviewing the fairly extensive literature on epidemic hepatitis has been considerably facilitated by the conscientious compilations and critical comments made in the thirties by several prominent authors such as WALLGREN (1930), BERGSTRÖM (1934), WICKSTRÖM (1936), THUNE ANDERSEN (1938), FINDLAY (1938) and SELANDER (1939).

On the face of it one could hardly expect the fairly unanimous conclusions reached by these my predecessors to be challenged seriously, but the experiences from the county of Västerbotten, especially as regards the epidemiology of the disease, are so peculiar as to motivate a renewed analysis of at least some of the earlier evidence. Before undertaking such a detailed scrutiny it seems appropriate to make an inventory of the points on which our present knowledge of epidemic hepatitis is admittedly deficient or contradictory.

When trying to form an idea regarding the risks of contracting an infectious disease at different ages one is usually content to work out the percentage of the sick in different age groups.

Such figures are obviously of little value as evidence. The proper way of course is to calculate the ratios between sick persons and persons exposed to risk in the different age groups and state the percentage of cases in these various groups. That this has not been done before presumably depends on the difficulties in estimating the size of a population among which an epidemic is considered to be prevalent and to decide how many individuals in such a population have been exposed to the risk of infection.

Because it has been impossible to compile such data the assertion that *children* are particularly susceptible rests on fairly feeble foundations.

On the question of *etiology* almost all authors postulate some kind of infection, but BRUGSCH maintains, that decomposed food-stuffs are responsible. Attempts at transmitting the disease to animals have failed or been inconclusive. THUNE ANDERSEN's

remarkable discovery that hepatitis could be produced in pigs with material from jaundice patients has not been followed up by an investigation into the nature of the pathogenic agent.

The mechanism of infection represents a two-sided problem. How is the contagion transmitted from one person to another and by which route does it reach the liver? On this point we shall find a disagreement between the generally held opinions and the evidence of the present investigation, and accordingly the premises on which the assertions on this subject have been founded must be reexamined. I am now going to review the literature on the first point, the mode of transmission, and later on I will try to tackle the second point.

LINDSTEDT who by his deductions regarding the time of incubation holds the title as pioneer among the students on the epidemiology of the disease, for which he has coined the name of epidemic hepatitis, does not commit himself to any statement regarding the mode of infection. Lindstedt's first series comprises 6 persons in a rectory who all came down with jaundice inside a month. This suggests a common source of infection and the medical officer of the district provides the information that jaundice was fairly widespread at the time. In such circumstances certainly a rector's family is particularly exposed. The local doctor, however, was more inclined to suspect the water supply and volunteered the information that wells in the district threatened to dry up. In the second series 5 persons took ill also inside one month, one of them being a schoolgirl aged 11, in whose school about 30 cases of jaundice were said to have occurred some months previously. The school epidemic might be explained as due to contact but school hygiene and in particular drinking arrangements being what they are in many rural schools the possibility of the contagion having been transmitted by water cannot be excluded.

The cited examples from the fundamental epidemiological work on hepatitis illustrate well the ambiguity of the evidence in most hepatitis epidemics and explain the conflicting views on the mechanism of infection held by different authors.

Since WALLGREN introduced the seasonal variation into the discussion by comparing incidence graphs in epidemic hepatitis with such graphs in epidemics of diseases which are spread by contact or ingestion respectively, several Scandinavian authors (Wickström, Bergström, Selander) have followed his lead. The con-

clusions reached by these workers are unanimously considered to favour the theory of contact infection. Wickström, however, quoting his Porlön summer epidemic, points out that a local outbreak might take place at any season and that confusion may result from single observations.

BELLANDER is not prepared to accept the seasonal distribution as proof of contact infection and points out that the graphs representing these variations of infection by contact as well as by ingestion are subject to modifications due to various circumstances, such as altered times for school attendance, improved hygiene and vitamin supply.

When comparing the seasonal graphs from the different authors a certain common tendency between them is certainly discernible but in detail notable differences are conspicuous. WALLGREN'S curve representing the seasonal distribution of case incidences 1925—1926, shows a maximum in November, while this is reached already in October in SELANDER'S compilation from 1931—1937. BERGSTRÖM also reports a peak in October. This precession of the maximum in later and bigger statistics does not convey the impression of a preeminently winter epidemic characteristic of Wallgren's analysis.

A circumstance which apparently has been overlooked in comparing graphs of different epidemics is the time of incubation in the various epidemics. When allowance has been made for the proven long time of incubation in hepatitis we are faced by a remarkable resemblance not to scarlet fever and diphtheria but to typhoid, dysentery and infantile paralysis. (Cp. Selander.) Wallgren's comparative graphs show the peak in the 1918—1919 typhoid epidemic to have been reached in October or during the same month when Bergström registers the greatest number of hepatitis cases in Gotland 1929—1932 and Selander in the whole of Sweden 1931—1937. The seasonal morbidity variations in epidemic hepatitis do not constitute a strong argument against transmission by ingestion.

The apparent ease by which the disease is said to be transmitted has also been underlined by several authors (WALLGREN, BERGSTRÖM, WICKSTRÖM, BATES, LISNEY, MAITLAND, CULLINAN, NEWMAN, McFARLAN) but comparatively few case records have been published substantiating the assertions. The objection that presumably several opportunities for infection present themselves during an outbreak is hard to refute. By showing that return

eases in hepatitis are considerably more frequent than in certain other diseases, Selander has provided the strongest argument so far presented in favour of the contact infection theory, especially with regard to sporadic cases. When trying to explain the frequent occurrence of absolutely isolated cases Wallgren and others assume »healthy carriers» to play a part. However, no definite evidence has yet been produced of their existence in epidemic hepatitis. This assumption is merely made because otherwise it is very difficult to explain some cases as due to contact. On the whole the opinions expressed concerning the infectivity as a rule are more conjectural than founded on substantiated observations. Some of the published data seem actually to indicate low infectivity by contact, for instance Wickström's Tesjö school epidemic, where only the Finnish children contracted the disease while the Swedish pupils escaped in spite of close proximity between the two categories during play. BASHFORD reporting on an departmental outbreak among post office employees has not been able to find one single contact case in the families of either of the 48 jaundiced cases. BELLANDER refutes the conclusion reached by Wickström and others that the simultaneous propagation over extensive areas should be incompatible with an ingestive infection by stressing the importance of improved communications and extensive distribution of victuals, and continues: »A droplet infection lasts a couple of months and seldom skips intermediary stations. Infection by ingestion has caused greater or smaller explosive outbreaks in connection with a well or water courses. We will now find another type, spreading slowly but obstinately, gaining a firm foothold in this place and passing by that. A characteristic feature of this mode of infection appears to be the small explosive outbreaks in families. Hepatitis shows this mode of propagation.» (Transl. by author.)

Many of the authors who have declared themselves to be of the opinion that hepatitis is a contact infection discuss more or less thoroughly the possibility of infection by ingestion. Thus Wallgren summarily rejects the idea of an alimentary infection in the same sense as typhoid or cholera. Wickström, Bergström and several British authors pronounce the water to be »not guilty», on what appears to Bellander to be deficient evidence. According to the latter the accumulation in families of several almost simultaneous cases, which is so frequently met with in epidemic hepatitis, suggests an infection transmitted by water.

He adds prophetically: »Greater explosions can only be expected in closed institutions. Particularly unfortunate circumstances such as an infected water main or infected food in canteens etc. are required to give rise to such outbreaks.»

It is obvious to anybody possessing a first hand knowledge of the hygienic conditions prevailing in the greater part of the rural schools in Sweden that the alternative of an infection by water or food in schools cannot be ruled out off hand as Wickström is inclined to do.

OLIN in a recent review on epidemic hepatitis maintains that waterborne epidemics of this disease have not been described. This is a remarkable statement considering that he himself in a report 1937 on an outbreak, investigated by him, to the Royal Medical Board admits the possibility of a waterborne infection, although in his opinion the beginning of the epidemic in January makes this interpretation less likely. Bellander who apparently has had access to the report in question points out that although contact had been shown in 18 cases out of 29, 22 could be related to polluted water.

The Österby Bruk outbreak reported on by Olin is by no means unique. In the same year the report on the Sunnanå epidemic referred to later in this paper must have been brought to his notice.

CARL LUNDGREN (1931) published a synopsis of the reports concerning hepatitis forwarded by the medical officers under his orders. Most of these accounts do not admit of any conclusions regarding mode of infection but the outbreak related by Hirsch is obviously due to water infection and therefore merits recapitulation. Among eight families all living in one barrack and drawing their water from the same well 12 persons took ill with hepatitis during May—December 1930. In the adjacent three barracks which had controlled water laid on, only one case of hepatitis occurred.

BELLANDER has been quoted rather extensively on account of his stimulating critical reviews; the essential importance of his paper, however, is a detailed survey of an outbreak of epidemic hepatitis in the industrial village of Surahammar 1939—1940. The author produces evidence that at least 77 out of 131 cases could be considered to have been infected by water from notoriously insanitary wells. Here as elsewhere whenever an epidemic is investigated which might also be propagated by contact it is

difficult to assess the importance of the aerogene or droplet infection.

One of the best authenticated descriptions of a hepatitis outbreak undoubtedly transmitted by water is given by R. FRASER. His original paper unfortunately has not been available but a brief review (in the *Kongr. Zbl. f. inn. Med.*) gives the outlines of the story. The epidemic visited a university town in Canada. Among 620 students living in, 600 suddenly fell ill with gastroenteritis. Agglutination tests indicated a *Salmonella* infection. Only a few cases occurred in the town population and these had used water from the well of the university. 2—5 weeks later 173 out of the 600 contracted typical hepatitis.

GLOVER and WILSON have investigated a school outbreak of considerable interest. It occurred in a town of some 6,000 inhabitants in which three boarding schools are situated. Two of these are boy schools with 400 and 50 boys respectively, the third is receiving 250 girls. Scattered cases of jaundice appeared in the town as well as three in the boy schools in March. The total number of cases in the town during the time March—June is estimated at between 200 and 300. From June 3rd until July 4th 32 boys caught hepatitis, the cases being fairly regularly distributed throughout the month, thus on an average about one a day. On July 14th an explosive outbreak took place, 13 boys falling ill; the following day another 13 took ill and on the 16th, 9. Inside a fortnight an aggregate number of 95 cases was counted.

The girls escaped completely although one of their mistresses took ill, presumably infected in the town.

The earlier more sporadic cases observed in June were frequently combined with tonsillitis (10 out of 32) which seems to have been interpreted as an initial symptom significative of contact infection. An accumulation of cases in certain dormitories was considered to be pointing in the same direction. A more plausible mode of infection seems to be the swimming bath used by boys from both schools but not at the disposal of the girls. The June cases probably have infected the bath to an increasing extent and a month later the explosion took place. A deglutition of infected water from the swimming pool certainly appears to be the likeliest explanation of this violent outbreak.

YENIKOMSHIAN and DENNIS have observed an epidemic of hepatitis in a Lebanese village. 37 cases were distributed fairly evenly during four months. Water was supplied from a covered cistern



to practically all inhabitants. Bacteriological examination revealed a heavy contamination of the water by intestinal bacteria, which disappeared after chlorination. No hepatitis cases were reported subsequently. A water infection must be suspected.

Recapitulating it is remarkable how nearly all the epidemics believed to support the theory of ingestion, have occurred in closed and demiclosed institutions, such as sanatoria, boarding schools, barracks etc. Obviously it is easier to assess the different possibilities inside a limited area, where the hygienic and sanitary conditions can be closely investigated. When an epidemic disease gains a foothold in a wider area the continuously changing interplay of cause and effect produces increasingly complicated conditions which are hard to judge except after thorough personal field work.

Even if, as has been shown, some epidemics of hepatitis have been found to have been transmitted by ingestion the fact must be kept in mind, that by far the great majority of investigators are adherents of the contact hypothesis. That such a mode of infection operates in sporadic cases has, as stated before, been shown by Selander and it can be reasonably maintained, that such contact cases should occur during an epidemic as well. Of course, the unanimous opinions expressed must carry some weight but it must also be stressed that quite definite proofs of contact infection as being of supreme importance are lacking in the published accounts. Many of the published papers are based on notifications and second hand information and do not contain detailed analysis of case histories. In such circumstances the question must be left open.

Maybe there is a tendency to be too dogmatic about contagious diseases; some of them are transmitted by contact, others — and in particular the enteric fevers — by ingestion of water or victuals. In both cases exceptions naturally occur. Thus even in typhoid we meet with occasional contact infections and some diseases generally spread by droplets might occasionally be transmitted by other agents. The sorting of the diseases into well-defined groups according to modes of infection is dictated by considerations of the practical measures to be taken in order to prevent outbreaks. This does not exclude the possibility that certain diseases do not fit into the hard and fast scheme but might perhaps be propagated for instance to the same extent by contact and water. There is also always a possibility that a

disease might behave in different ways in this respect at different seasons of the year. Considering that the question concerning the mechanism of infection in epidemic hepatitis has not yet been definitely solved, it is incumbent on us to explore every logical possibility and accordingly to postulate a propagation of the disease in alternative ways.

Owing to local conditions one or the other of the types of infection enumerated above might predominate.

The theory of contact infection could not be accepted without some explanation of how the virus is excreted and assimilated and by which route it eventually reaches the liver. Wallgren has met the demand in elaborating a working hypothesis which has been generally accepted and quoted by subsequent authors. According to him the contagion enters as well as leaves the body by the way of the nasopharynx from where it is carried to the liver by the blood stream. To the extent to which hepatitis is at all spread by contact — and this appears in particular to be the case in the sporadic cases with proven longer time of incubation (Selander) — the hypothesis fits the facts well. Some authors, however, Bergström, Glover and others seem inclined to consider the appearance of an initial sore throat as indication of a nasopharyngeal entry of the contagion, which hardly can be the case considering the long time of incubation.

Interesting observations on unusual transmission of hepatitis have been published off and on since 1925, when FLAUM, MALMROS and PERSSON made it likely that a nosocomial epidemic of hepatitis among diabetics had been caused by inoculation with infected instruments at the laboratory. Later STEINITZ and LINDSTEDT have recorded similar outbreaks. In his paper on the subject Lindstedt hesitates about accepting inoculation as the means of transmission, because the observed long incubation times do not agree with those found by himself and other writers. In fact they must, however, be said to conform excellently with the incubation times, found by Selander to be characteristic in sporadic cases. The of necessity feeble dose administered by contact and inoculation could be thought to require a longer time before giving rise to clinical symptoms. Further evidence of infection by inoculation has been produced by PROPERT and MAC NALTY who saw the disease break out after the administration of convalescent serum against measles, as well as by FINDLAY, MACALLUM and MURGATROYD who experienced an outbreak among persons inoculated

with vaccin against yellow fever, of which human serum formed a constituent part. The latter outbreak has been of considerable scientific importance in as much as by its investigation it has been possible to obtain conclusive proof of the virus nature of the hepatitis contagion.

Struck by the similarity between the pathologic-anatomical pictures in yellow atrophy of the liver and in glomerulo-nephritis, Bergstrand has asked himself whether streptococci might not also be the cause of hepatitis. At post mortem examinations he was able regularly to isolate strains of streptococci of the viridans type from the intestine. These, however, were never found to be pathogenic when administered to different experimental animals. Wallgren also has tried to discover the virus by biological methods using rabbits and guinea pigs but reports failure. More or less thoroughgoing etiological research work has been carried out in connection with the investigations into most of the epidemics reviewed above. Both bacteriological and biological methods were used on various material from hepatitis cases, such as stomach and nasopharyngeal washings, duodenal juice, serum, urine, faeces, etc., employing a great variety of experimental animals. Findlay for instance reports on experiments with 13 different animal species, among them mice. Yenikomshian too made use of mice as well as rabbits and guineapigs. In no instance has success been claimed until ANDERSEN was able to produce distinctly pathological alterations in the livers of pigs by feeding them duodenal juice obtained from hepatitis cases.

When we turn to the clinical aspects of the disease the interrogation marks abound. In spite of the fact that a great variety of tests have been applied as a routine in examining the patients everywhere — as the numerous casuistic notes broadcast throughout almost every paper on the subject prove — one might search this literature in vain for intelligent analysis of even simple and obvious symptoms. An outstanding exception, however, is Selander who in his comparative study on sporadic and epidemic hepatitis has investigated closely some aspects of the symptomatology. As a rule, however, the initial stages of the disease have not been observed because the patients have not been admitted to the wards until later.

In the present work the author has endeavoured to make a contribution to the present knowledge of epidemic hepatitis by

collecting and estimating facts as well as by conducting experiments on the following more or less unexplored points:

- 1) The mode of infection.
- 2) The general susceptibility as well as the morbidity in different age groups.
- 3) The time of incubation.
- 4) The nosography of the initial stage.
- 5) The duration of the preicteric stage.
- 6) The extent and duration of the disturbance in the distribution of bile pigments in the body brought about by the disease.
- 7) The general physiological repercussions of the disease as indicated by various current clinical tests.
- 8) The effects of the disease on the composition of the blood and on the functions of the kidneys.

## Material and Methods.

The present work deals exclusively with conditions in the county of Västerbotten in northern Sweden. This roughly rhombic area of 59,148 square kilometers stretches as a 200—250 kilometers broad belt in a SE—NW direction from the Bothnian gulf to the Norwegian border, across the southern parts of the provinces of Västerbotten and Lapponia between Lat. N.  $63^{\circ} 30'$  and  $66^{\circ} 30'$ . The population on December 31st 1939 numbered 218,418 or on an average 4.0 to the square kilometer. From a glance at the map it will be gathered that the density of the population varies considerably, the coastal plain and the river valleys being comparatively thickly settled as contrasted with the scattered colonisation of the inland plateau and the mountainous backbone of the Scandinavian peninsula. (See map.)

For the purpose of public health the county is divided into 26 districts, each in charge of a district medical officer (D. M. O.). These districts correspond to the rural parishes. The two towns form medical districts of their own. As responsible administrative and coordinative head of the medical service acts the medical officer of health (M. O. H.).

Demographic figures have been culled from the Statistical Yearbooks and from the M. O. H.'s annual reports.

### Epidemiological.

The table registering the prevalence of epidemic jaundice has been compiled from the fortnightly reports of the D. M. O.s'.

The detailed information regarding the Hällnäs epidemic has been extracted by the author from case records at the sanatorium and from the notes of the D. M. O. in the Vindeln district.

The D. M. O.'s of Skellefteå and Vilhelmina have contributed available material from their respective districts.

Bacteriological examinations of suspected water have been carried out at the Bacteriological State Laboratory in Stockholm (professor C. Kling).

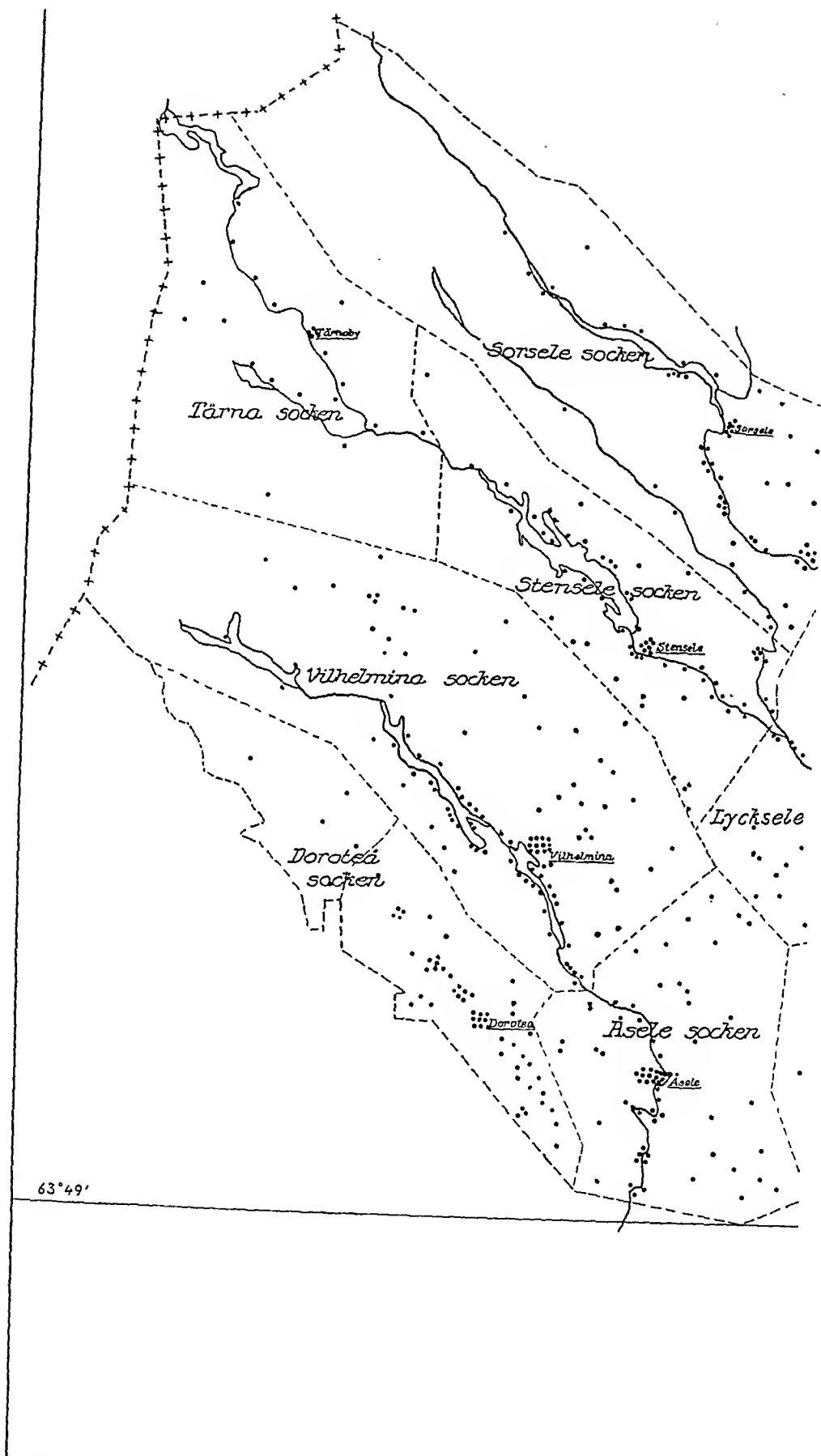
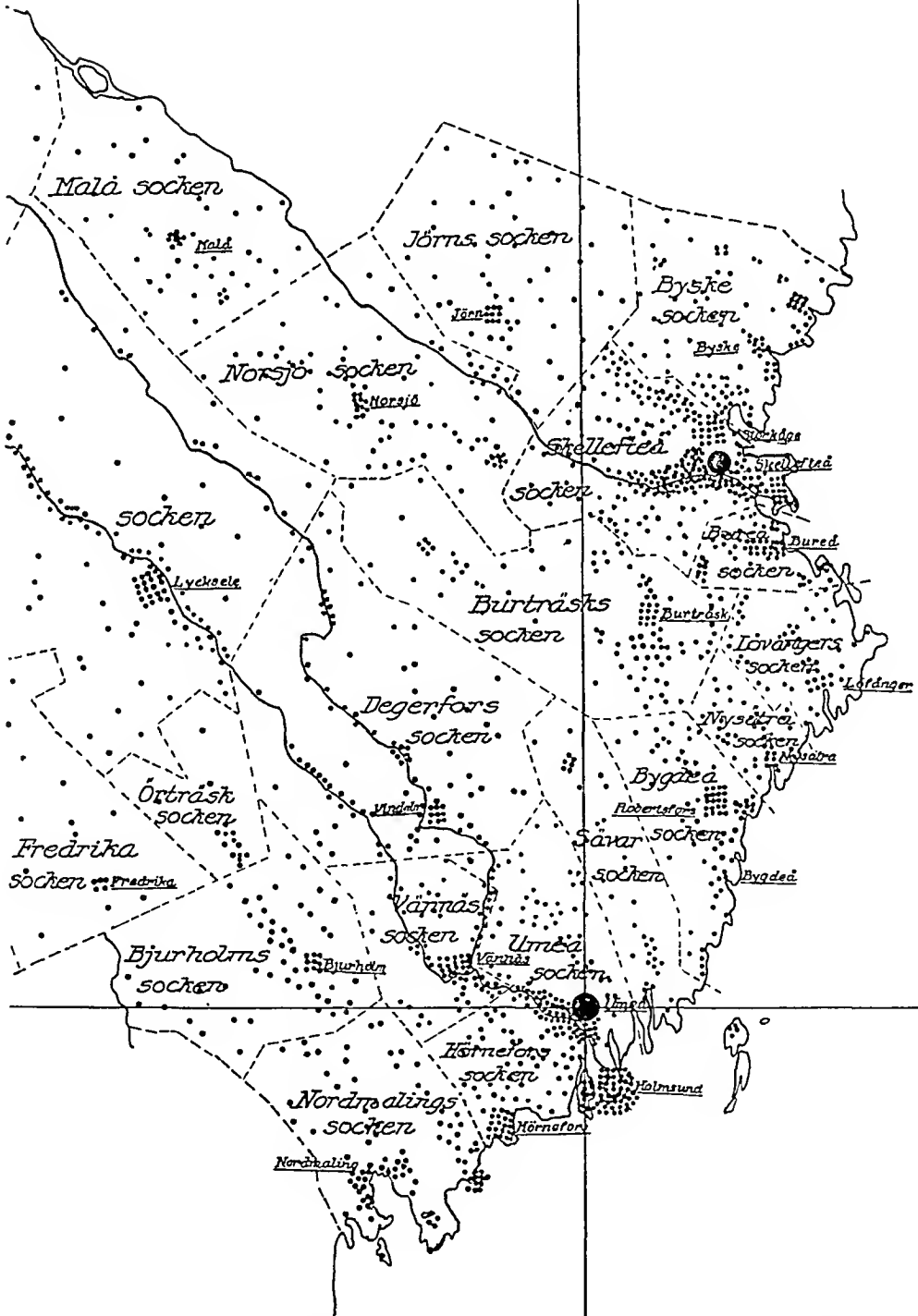


Fig. 1. Map of county of Västerbotten showing division into districts  
 befolkningens fördelning i Sverige 1 januari 1917). Population

- Each black point represents 100 inhabitants.
- Town with a population of 8294.
- Town with a population of 13465.



and distribution of population according to Sten de Geer (Karta över figures approximately corrected for the date of January 1st 1938.

The investigation into the occurrence of porcine hepatitis has been conducted by the county veterinary surgeon (C. V. S.) with the assistance of district veterinary surgeons and veterinary surgeons employed at the meat control stations.

## Clinical.

The clinical facts worked up and analysed in the present paper are derived from 178 cases among the sanatorium population in Hällnäs. The composition of this population at the onset of the epidemic as well as subsequent changes during the time under review has been recorded in table 5 together with the corresponding analysis of the hepatitis cases.

Besides giving information regarding sex and age distribution the table refers to three distinct categories, i. e. patients, staff and family members of employees. Special consideration has been given to the coincidence of tuberculosis and hepatitis in the following chapters.

In order to complement certain clinical dates not provided by the Hällnäs material extracts were made from the records of 149 uncomplicated cases of hepatitis, treated in the medical wards of the Central County Hospital in Umeå during the years 1937—1941.

## Case histories and nosography.

Patients records are very exhaustive about everything having a bearing on tuberculosis and give a fair idea about the general health of the patient at monthly intervals but detailed notes on the symptomatology of the nosocomial hepatitis infection are less comprehensive and show variation as regards detailing of subjective complaints such as headache, itch, nausea and so on. Frequency and consistence of stools as well as the occurrence of vomiting, however, are by routine being entered on the temperature graphs.

Personnel are subject to medical examination before employment and their health cards indexed. In case of illness notes are being entered on the health cards. These notes, however, are less detailed than those found in the case records and as a rule give no information regarding minor discomforts.

Family members of employees have been attended by the house physicians during their jaundice illness and rough notes not containing any reference to subjective complaints have been kept.



With regard to objective observations and in particular the different tests for bile pigments in serum and urine, all three categories have been examined to the same extent and results carefully registered. Five patients who took ill with jaundice after their discharge or when on leave in their homes have not had any laboratory tests made. In two instances the notes have been lost.

### Laboratory tests.

*Blood:* All patients have the suspension stability of their erythrocytes tested at intervals of 3 weeks. The method is that described by Westergren, the readings being made after one hour. Staff and family have not been tested.

Haemoglobin estimates and counts of red and white cells have been made at irregular intervals employing respectively the Zeiss-Icon haemoglobinometer and the Bürker counting cell. Differential counts of white cells form no part of the routine. Ten such counts have been made, however, in three jaundice cases among previously healthy personnel, the films being stained according to May-Grünwald and 200 cells counted. The same technique has been employed at the Umeå hospital.

*Bile pigment* in blood serum has been measured by the method recommended by Meulengracht at weekly intervals in jaundice cases of all categories at Hällnäs. At the Umeå hospital qualitative and quantitative estimates of serumbilirubin have been carried out according to Hijman van den Bergh and liver function judged by the galactose assimilation test. As a side issue to the clinical survey, an investigation into the normal values of the Meulengracht test and their variations was carried out on blood serums from healthy persons volunteering as blood donors.

*Urine.* The urine of the sanatorium patients is regularly tested for albumen and glyucose by the Heller and Almén tests. Sediments are being examined microscopically in such cases where the Heller test reveals the presence of albumen. Diazo tests have been carried out in a great number of cases.

The presence of bile pigments has been established by employing the Iodine test and the Schlesinger tests for urobilin and urobilinogen. In a limited number of cases the Hammarsten reaction has been substituted for the iodine test. All tests have been uniformly carried out according to the technique usually employed at Swedish hospitals, i. e. according to the directions given by Lisa Broström in her manual of laboratory technique.

Blood sample from one jaundice case treated at the medical clinic of the Central Hospital in Umeå has been sent to the central laboratory of the Sahlgrenska Hospital in Gothenburg (Professor Lehman) for estimation of citric acid and phosphatase in serum.

In order to realize whether a patient, who had been ill with symptoms of acute indigestion but where jaundice never had been observed and who could be suspected of having introduced the infection into the sanatorium showed signs of impaired liver function indicative of hepatitis, similar tests were carried out at the same laboratory.

### Statistical methods.

Current statistical methods and formulae have been employed in the statistical analysis. The standard deviation,  $\sigma$ , is calculated according to the following formulae:

$$\sigma = \pm \sqrt{\frac{\sum a^2}{n-1}},$$

where  $a$  indicates deviation from the mean and  $n$  the number of observations. When  $n$  exceeds 50 the following formula has been used:

$$\sigma = \pm \sqrt{\frac{\sum a^2}{n}}.$$

The standard error of the mean  $\varepsilon(M)$  is computed according to the formula:

$$\varepsilon(M) = \pm \frac{\sigma}{\sqrt{n}}.$$

The standard error of a percentage  $\varepsilon(p)$  is obtained by means of the formula:

$$\varepsilon(p) = \pm \sqrt{\frac{p(100-p)}{n}},$$

where  $p$  is the percentage and  $n$  the number of observations. The standard error of a difference  $\varepsilon(D)$  is calculated according to the formula:

$$\varepsilon(D) = \pm \sqrt{m_1^2 + m_2^2},$$

where  $m_1$  and  $m_2$  indicate the standard errors of the means in question.

# Epidemiology.

## General Review.

Although epidemic jaundice was not made notifiable until 1931 it could be expected that epidemic accumulations of jaundice cases would have attracted the notice of the health officers, and one would accordingly expect to find references to the disease in their yearly reports. A looking up of back numbers of the yearly reports from the medical officers of health shows that this has been the case.

»Icterus catarrhalis» is first mentioned in 1897 when an epidemic spread during the summer months had been observed in the district of Åsele. The following year 8 cases were reported in the Nysätra district as well as an undefined number of cases in the adjoining Bygdeå district. In the following 15 years no reference is made to the disease, but in 1913 more than 100 cases of pronounced epidemic character are said to have occurred in the district of Stensele. In 1915—1916 the disease is reported to have been common in Åsele and Dorotea. In 1918 several cases appeared during the spring in Skellefteå, and in the same year the cases in the Vindeln district were so numerous that the district medical officer ventures the opinion that an infectious form seemed likely. Next time any reference is made is for the year 1928 when the district medical officer in the Umeå rural district reports a great number of cases »of obviously contagious jaundice» during the autumn in particular in Holmsund and the villages surrounding the town of Umeå.

As notification of cases of jaundice became compulsory in 1931, but no cases — except 13 in 1933 — were notified until 1937, it might be assumed that no other such cases have become known to the doctors in Västerbotten in the intervening years.

During the time under review, i. e. from April 1st 1937 until the last of June 1941, a total of 1,187 cases of hepatitis have been notified. It is impossible to say to what extent the registered cases represent the actual morbidity. On the one hand one would

expect that in urban and suburban areas with accumulated populations and medical advice within easy reach, the doctor would be called in to see most of the cases of a disease which after all starts with rather alarming symptoms and runs a prolonged course with considerable affection of the general status of the patient, whilst on the other hand in sparsely populated rural districts the doctors fees might act as a deterrent. It might also be argued, however, that a population which becomes familiar with a disease on account of an epidemic accumulation of cases in a comparatively confined area, quickly learns to recognize the nature of the ailment and having gained by experience from neighbours some idea about its general course and apparently harmless nature desists from seeking medical advice, whereas isolated families scattered in a rural district might more readily become alarmed by the rather dramatic onset of this particular illness. It might perhaps be safe to assume that the different factors discussed fairly outweigh each other so that the notified cases to a reasonable extent reflect the actual prevalence of the disease in densely as well as in sparsely populated areas.

A scrutiny of the tables 1 and 2 and graph 2 reveals that the epidemic started in the rural district of Skellefteå, and as will be further expounded later in the suburban village of Sunnanå. From there it spread in the first place to the town of Skellefteå across the river and later to the adjoining rural districts. Practically all cases during the latter half of 1937 and the first half of 1938 occurred in the northern part of the county surrounding Skellefteå, and these districts have been practically free from the disease since the middle of 1938. With regard to the concentric spread round the first centre of outbreak in Sunnanå, the distances measured along the different roads converging on Skellefteå do not correspond to the maximums of morbidity as represented by the medians. This, however, has no significance, because there is a considerable difference with regard to communication facilities between Skellefteå and the different rural district under review, and also with regard to the density of population along the different roads, some of which run for miles on end through uninhabited woods while others, for instance the coastal roads, wind through almost adjoining minor villages. Anyhow, as pointed out, a certain centripetal spread concentrically from the first outbreak can be traced with regard to the Skellefteå region in 1937—1938.

TABLE 1.

Distribution of notified cases of hepatitis on the different districts during different months and years (1937—1941).

District		1937									
		IV	V	VI	VII	VIII	IX	X	XI	XII	
1	Skellefteå rural				7	43	59	38	19	15	
2	„ town					8	34	31	30	10	
3	Jörn	2		1	1	1		11	2	2	
4	Nysätra					1	2	2	3		
5	Boliden						4	4	11	1	
6	Byske							8	11	12	
7	Norsjö						1	2	5	3	
8	Lövånger						2	2			
9	Bureå						5	13	6	8	
10	Burträsk							6	4		
11	Kågedalen						1	2			
12	Bjurholm										
13	Robertfors										
14	Stensele										
15	Vihelmina										
16	Umeå town										
17	Åsele										
18	Umeå rural								2	1	
19	Vännäs										
20	Vindeln							1			
21	Hörnefors										
22	Lycksele										
23	Malå										
24	Sorsele										
25	Tärna										
26	Nordmaling										
27	Holmsund								1		
28	All districts	2	—	1	8	53	108	120	94	52	

435

The subsequent cases seem to be scattered quite irregularly over the county. Two areas seem to have been more or less totally unaffected, one represented by the south eastern part of the county, including the districts of Hörnefors, Nordmaling and Holmsund, the other represented by the major part of the laponian area, this latter, however, with the important exception of the district of Vilhelmina where a certain number of cases have been reported during most of the months from 1939 onwards. The

Table 1 (continued).

Distr. no.	1938											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
1	13	6	2	2			1		2	3	2	
2												
3												
4	2	1										
5	9		2				1					
6	5	2	1	1		1						
7	2	2										
8	5											
9	8	6	8	2				4	3	1		
10	11	4	7	1		1			1			
11		2			1					1		
12												
13		9					3			2	4	2
14												
15									3	3		2
16		1	4	1					4	1	1	2
17												
18	5	1			1	1			1		1	1
19												
20											5	
21												
22												
23									1			1
24												
25												
26												
27		1										
28	60	35	24	7	2	3	5	4	15	11	13	8
131						56						

arrangement of the districts in this middle group according to the medians of the cases does not give any clue to the mode of propagation of the disease when compared with their geographical position and means of communication. To judge by the medians, however, a certain tendency of a spread from the coast inwards against the flow of the rivers might be noted.

It is beyond dispute that we have to deal with at least two distinct accumulations of hepatitis cases which must be characterized as epidemics. It is the Skellefteå epidemic and the Hällnäs epidemic, both having peculiarities of their own which will be the main subject of the present work and accordingly dealt with

Table 1 (continued).

Distr. no.	1939											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
1												
2												
3												
4												
5												
6												
7												
8												
9		3	1				1					
10												
11												
12	5	3	2									
13	1	7	3	4	1	1			1		4	
14					3	1	4	2				
15			4	3	4	2	1	2	7	8	2	7
16				4					2	4		
17				1								
18	2	2		4		1					3	
19			1		1						4	2
20												
21												
22												
23												
24												
25												
26										1		
27												
28	8	15	11	16	9	5	6	4	10	13	13	9
64				55								

exhaustively later. In addition I feel inclined to consider that the hepatitis morbidity in the districts of Robertsfors, Vilhelmina and Vännäs has been of a magnitude to permit of characterizing the disease as being epidemic. With regard to the rest of the districts, however, the few cases scattered over several years are more suggestive of the sporadic distribution as indicated by Selander. It must also be borne in mind that the notification reports do not admit of any specific localization of the particular cases inside the frequently very extensive areas covered by the different districts. The cases might be scattered over many square miles or be crowded into a village. Thus an incidence figure

Table 1 (continued).

Distr. no.	1940											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
1							1		1			
2												
3												
4												
5												
6							1				1	
7								1	1			
8												
9				1								
10												
11												
12												
13		2			1		1					
14												
15	1			1	4	12	9	5	1	2		
16	1			4		2	2		1	5	7	
17	1	2	4	3	4	3	3	3	4	1		
18	1			5	3		2	3	6	3	4	2
19		4	1			13	4			1	2	1
20							2					
21				1								
22												
23												
24												1
25												
26												
27												
28	4	8	5	15	12	30	25	12	14	12	14	4
	74						81					

might at one time indicate several 'sporadic' cases, at another time refer to a minor local epidemic in a single family or in a few neighbouring houses.

When dividing up infectious jaundice in epidemic and sporadic cases the latter group obviously cannot always be considered to be homogeneous, because jaundice might develop in connection with various diseases. Of greater importance is the question whether we have to deal with a specific type of sporadic hepatitis in some way distinguishable from the epidemic variety or with chance variations of the same disease ranging between single cases and larger epidemics.



Table 1 (concluded).

District		1941						1937-1941
		I	II	III	IV	V	VI	
1	Skellefteå rural							214
2	"      town							113
3	Jörn							20
4	Nysätra							11
5	Boliden							32
6	Byske							43
7	Norsjö							17
8	Löfånger							9
9	Bureå					1		71
10	Burträsk							35
11	Kågedalen							7
12	Bjurholm							10
13	Robertsfors							46
14	Stensele					1		11
15	Vilhelmina	1	1	1	5	2	1	94
16	Umeå town	1	2		3	1	4	57
17	Åsele					2		31
18	Umeå rural		5	1		5	4	70
19	Vännäs	11	12	9	8	3	2	79
20	Vindeln		25	29	116	10	7	195
21	Hörnefors							1
22	Lycksele				1			1
23	Malå						3	5
24	Sorsele						1	2
25	Tärna					1	3	4
26	Nordmaling				4		2	6
27	Holmsund							3
28	All districts	13	45	40	137	26	27	1187

Selander distinguishes two separate diseases with differing times of incubation. He considers it proved that sporadic hepatitis has a very long stage of incubation. My material provides no contributions to this particular problem concerning the genesis of sporadic cases. There can be no doubt that my material is made up by epidemic hepatitis, but, as is shown by the tables, the extent of the different epidemics varies considerably. In some districts only comparatively few cases have been reported. In other words it is hard to say whether occasional cases of sporadic jaundice have been included.

A peculiar position among the different areas tabulated is

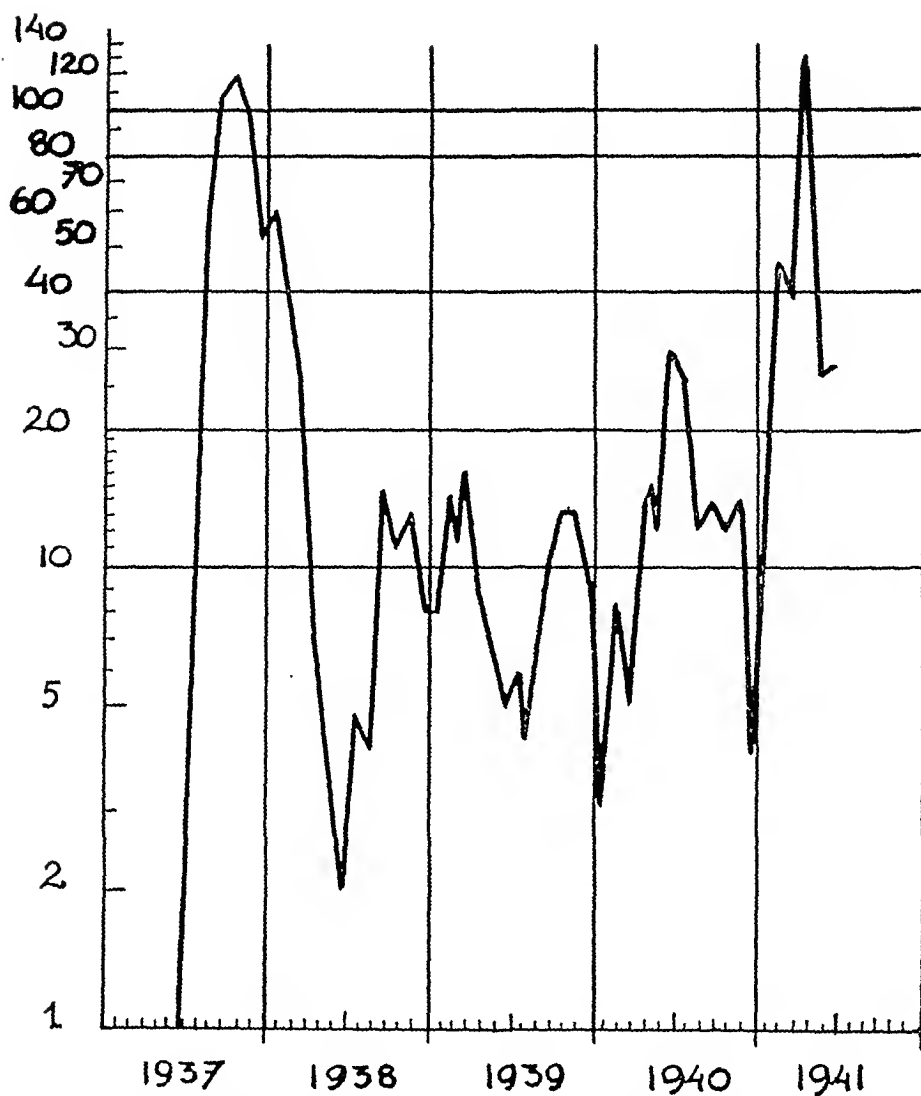


Fig. 2. Semilogarithmic graph representing number of notified cases of epidemic hepatitis in the whole county of Västerbotten during the time June 1937—July 1941.

taken up by the town of Umeå on account of it being the administrative, judicial, military, educational and hospital centre for the whole county, entailing an immigration of people, in particular of school and military ages from a vast area. To what extent the hepatitis cases notified from Umeå have been imported by this influx cannot be estimated.

The morbidity index worked out as number of hepatitis cases per 1,000 inhabitants might with due reservation for the entailed errors as discussed above give some idea about the prevalence of

TABLE 2.

Percentage, of. cases in the populations of different districts. Times for the local epidemics expressed in medians: Distances in km. from Sunnanå, where the first outbreak took place, to the centres of surrounding districts.

District	Number of cases	Population 31/12 1939	Pro mille	Medians	Kilo-meters
Skellefteå rural	214	17.249	12.0	30. IX 1937	0
» town	113	8.389	13.5	15. X »	1
Jörn	20	5.781	3.5	15. X »	61
Nysätra	11	3.803	2.9	10. XI »	72
Boliden	32	4.259	7.5	23. XI »	34
Byske	43	10.118	4.2	8. XII »	32
Norsjö	17	7.142	2.4	10. XII »	90
Lövånger	9	4.660	1.9	6. I 1938	52
Bureå	71	6.144	11.6	15. I »	20
Burträsk	35	10.005	3.5	22. I »	41
Kågedalen	7	4.571	1.5	15. II »	22
Total number of cases in the Skellefteå area	572	72.171	7.8		
Bjurholm	10	6.825	1.5	5. II 1939	
Robertfors	46	7.306	6.3	11. II »	
Stensele	11	6.585	1.7	15. VII »	
Vilhelmina	94	10.807	8.1	18. XII »	
Umeå town	57	13.160	4.3	8. IV 1940	
Åsele	31	8.139	3.8	10. VI »	
Umeå rural	70	22.883	3.1	8. VII »	
Vännäs	79	7.142	11.0	16. I 1941	
Vindeln	195	9.399	20.7	9. IV »	
Hörnefors	1	3.922			
Lycksele	1	11.957			
Malå	5	4.306			
Sorsele	2	5.828			
Tärna	4	2.117			
Nordmaling (Holmsund)	6 3	9.555			
Total number	1.187	212.052	5.5	3. X 1938	

the disease in the different areas. If so one could be inclined to adopt 6 ‰ as the limiting figure below which one would have to consider the cases to be sporadic. This of course provided that all the notified cases during the *whole* of the epidemic are included. The suggested limit of course is quite arbitrarily chosen and only warranted by a general impression of the prevalence

of the disease. The figures seem to change so gradually that they do not appear to suggest any marked difference between the epidemic and sporadic forms of the disease. Only further investigation built on research into possible etiological differences will be able to decide this issue.

Having surveyed the general prevalence of epidemic hepatitis in the county of Västerbotten as a whole the various local epidemics will now become the objects of detailed study.

### The Sunnanå epidemic.

As may be judged from table 1 the hepatitis epidemic started with an explosive outbreak in the rural district of Skellefteå, where in the suburban village of Sunnanå on the right bank of the Skellefteå river opposite the town of Skellefteå 7 cases of hepatitis were notified by the district medical officer during the end of the month of July, 43 in August, 59 in September and 38 in October.

The simultaneous mass infection seemed to suggest either a disease of the influenza type with short incubation and spread by contact or else an alimentary infection simultaneously exposing a large number of the community.

The time of incubation in epidemic hepatitis has been established by Folke Lindstedt and others and found to be ranging between 19 and 36 days. Provided that this epidemic was identical with those described by previous authors and running true to type with regard to incubation time an alimentary infection appeared to be the most probable. In such circumstances it is of interest to review the general sanitary conditions of the community where the outbreak took place.

The community of Sunnanå has developed by the coalescence of the two adjoining villages Sunnanå and Sörböle, see fig. 3, in which the dispersed rural house planning is gradually being superseded by settlements of a more suburban type. In 1937 the component parts of the community still derived their water supply from different sources. Most of the houses in Sunnanå proper are served by water pipes from the Skellefteå main, carrying unimpeachable water from the lake Falkträsket to the town, while the inhabitants of Sörböle had to rely on wells for their water supply. These wells are without exception very unsatisfactory from the sanitary point of view. They are shallow and insuf-

ficiently protected against pollution by surface water. During seasons of drought they run dry.

This was the case during the exceptional dry and hot summer of 1937. Thus deprived of their water supply, the inhabitants of Sörböle had to resort to the Skellefteå river. Owing to similar exigencies in earlier years a number of private conduits each serving a couple of the later erected houses had been installed by which river water was distributed to a great number of the households. On account of the considerable pollution of the river water, the county government had in 1936 prohibited its use for domestic purposes. This decree, however, was never conformed to.

According to the district medical officer by far the greater majority of the first reported cases of hepatitis occurred in the Sörböle part of Sunnanå, where river water was laid on, whereas in the beginning only a few scattered cases became known from the Sunnanå part of the community or from the town of Skellefteå opposite the river. This naturally gave rise to a suspicion that the contagion might be transmitted by water, and the situation seemed to call for a sanitary inspection. This revealed appalling conditions. Along the southern bank of the river a number of pump units had been installed. The suction pipes were carried out only a few meters beyond the low water level. No arrangements for filtering or chemical purification of the polluted river water had been made anywhere. The suction pipes were spaced out at different distances from each other, varying between 10—15 meters. Alternating with them were found a series of drains and waste pipes, carrying away the excretas of the village. These sewers were not carried out into midstream, but some ended at the same level as the water intakes, and some further inshore, forming stinking pools of rotting sewage in backwaters and eddies. In one particular place the greyish stream of sewage could be traced along its entire course from the sewer to the water pipe. As could be expected under such circumstances the samples from different household taps, belonging to the different »water works» showed high colititers, i. e.  $> 10,000$  coli per liter.

According to the accepted views of almost all authors on the subject at that time epidemic hepatitis was supposed to be transmitted exclusively by contact. On account of this conception no steps had been taken at the onset of the Sunnanå epidemic to chart and register the cases as well as one would have wished. The only dates now available have been collected from the notes

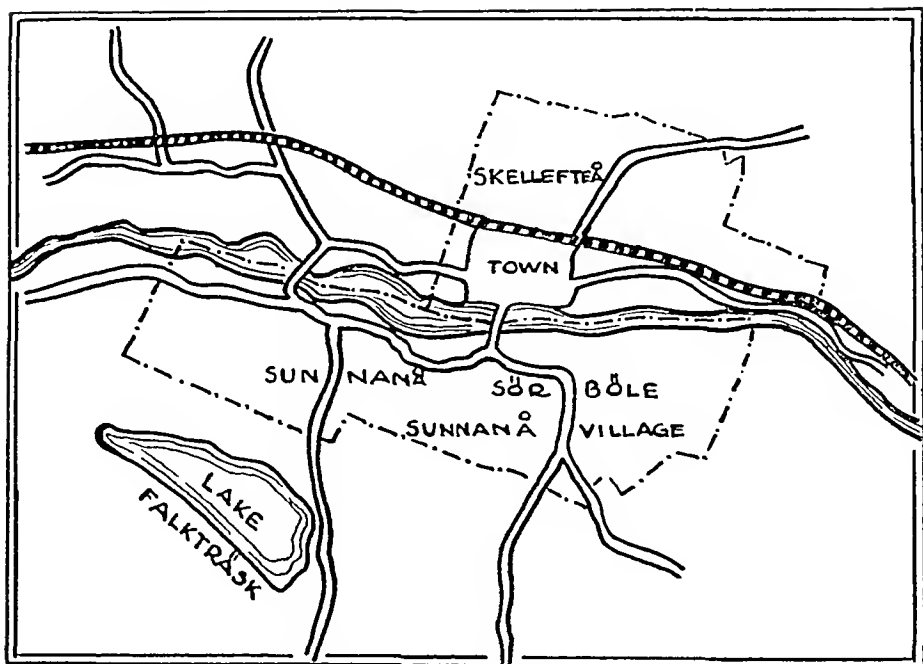


Fig. 3. Topographic map of the Skellefteå area.

of the district medical officer, from which may be gathered that all the 7 first known cases notified in July occurred in Sörböle, that out of the 43 cases notified in August, the 59 cases in September, the 38 cases in October; 27, 25 and 9 respectively occurred in Sörböle. Instead of carefully recorded facts one had to be content with vague general impressions, and by the time these seemed to point into the direction of defective water as the transmitter of the disease the suggestive, original, epidemiological picture had been blurred by the spread of the secondary mass infection to the adjoining areas. In such circumstances all one could do was to prevent further distribution of polluted water by enforcing the county government's prohibition.

The experience left a lingering feeling of a rare opportunity missed to probe into the secrets of epidemic jaundice and led to a firm resolution not to waste the next chance should it come my way. The conclusions, such as they were, together with epidemiological facts, were worked into a report to the Royal Medical Board by my successor as a locum tenens to the M. O. H. This report was submitted by the Royal Board to their scientific councillor on bacteriology, professor Carl Kling, who expressed as his opinion that the water infection theory was not likely, and

who quoting Thune Andersen's recent research suggested that an investigation should be carried out into the possibility of the epidemic, being due to infection by pork from pigs, suffering from hepatitis. Conforming to this suggestion a circular was issued by the county veterinary surgeon to all district veterinaries, exhorting them to pay special attention to the occurrence of hepatitis in hogs.

By far the greatest number of pigs raised in the county of Västerbotten are being slaughtered at the collective abattoirs at which organs are examined by specially trained veterinary surgeons. In spite of the special attention paid to the possibility of jaundice and hepatitis not one single case has been reported from any of the meat controlling stations in the county during the time 1937—1941, neither have any instances become known where living pigs have been found to be suffering from jaundice. According to reports 18,159 livers have been examined.

### The Vilhelmina epidemic.

More detailed information is given about two separate local accumulations of cases.

In the *home for the aged at Vilhelmina* with an average number of 35 pensioners and a staff of 7, 9 cases of hepatitis are reported between January 1940 and May 1941. Only one of the inmates came down with the disease, whilst the 8 other cases occurred among the staff. Thus: 3 attendants took ill within 1½ months, 1 within 2 months, 2 within 3 months and 1 case 5—6 months after taking up work at the institution.

The first case, an attendant previously domiciled in the village of Volgsele, joined the staff on October 1st 1939 and took ill with hepatitis in January 1940. She is unaware of contact with hepatitis cases either in her family or in her native village. In April one of her colleagues who had been employed at the almshouse for several years fell ill. Whether she has been infected by the newcomer or not, cannot be estimated.

The next 4 cases occurring at, on an average, monthly intervals, seem to suggest contact infections. During the last quarter of 1940 hepatitis was absent.

An attendant, employed on November 1st 1940 took ill with hepatitis in January 1941, and subsequently two other employees came down with the disease in March and May respectively.

Hepatitis has apparently been endemic in the home for the

aged at Vilhelmina, the young employees becoming infected about two months after their arrival.

The second accumulation occurred in the isolated crofter's cottage, *Valltorpet*, occupied by a family of eight of which five members took ill on respectively the following days; March 31st, April 12th, 21st, 22nd and 23rd 1941. In addition a relative paying a chance visit on April 11th subsequently caught the disease.

The infection had apparently been imported by two sons who had been working as lumber men in Skog where hepatitis was said to be prevalent at the time and who probably were in the incubation stage when they arrived home.

The fact that their sister who had not been away from home for months was the first to fall ill points in the direction that the disease might be transmissible during the stage of incubation.

Obviously the spread is facilitated by the intimate contact prevailing in an overcrowded house with poor sanitation.

### **The Hällnäs epidemic.**

In the last week of February 1941 the district medical officer of the district of Vindeln notified 25 cases of jaundice, all occurring almost simultaneously in the sanatorium at Hällnäs. On approach the medical superintendent confirmed the facts and gave the information that the cases had occurred at the same time, not only among the patients and nursing staff but in the doctors' families and in the households of other personnel living within the sanatorium precincts but having housekeeping of their own. Obviously the causal agent must have been administered at the same time to these separate categories of the sanatorium population.

The Hällnäs sanatorium of 340 beds and with an aggregate personnel, including families domiciled on the premises, of 135, i. e. a total population of 475, is situated on a sloping hill above the adjoining village of Hällnäs of 539 inhabitants.

The different sanatorium sections and wards are by no means to be considered as watertight compartments. Only about two thirds of the patients are permanently bedridden, whereas the rest are up and about most of the time, assembling at meals in the common dining hall and for recreation in the libraries, lecture halls and club rooms, thus providing opportunities for contact infection between patients from different wards.



The patients in each section have their lavatory facilities in common, making indirect infection at least theoretically possible. As there is a constant interchange of individuals between the category treated with restcures in bed and that formed by improving cases which are allowed to dress and move about for varying hours, it has been impossible to find out, whether there is any difference regarding hepatitis incidence in these two categories.

At Hällnäs, cases of hepatitis both among patients and personnel have been confined to bed immediately at the onset of illness, thus reducing the exposures to contact infections. Transmitting by contact ought primarily to have taken place in the wards, where nurses and sick attendants assisting the sick and handling their soiled linen and utensils were those most exposed, wardmates coming next.

There is a fairly lively communication between the sanatorium and the village, both personnel and patients paying occasional visits to the village for the purpose of shopping and so on.

The families of the sanatorium staff buy their food supplies in the village, whereas the sanatorium itself is victualled from wholesale dealers. Pasteurized milk and dairy produce is supplied to the sanatorium from the local dairy, whereas at least some of the families obtain unpasteurized milk directly from different farmyards.

Pork is provided from the pig herd raised on the sanatorial premises on offal from the kitchen which is boiled before being fed to the pigs. This boiled pig food contains by itself so much water that no additional water is supplied for drinking purposes. It might, however, be noted that the sties are being flushed with water from the reservoir, thus providing a possibility for the pigs to become infected, should the water be proved to be the vehicle of the infectious agent. So far there has been nothing the matter with the 35 pigs, and two batches of five killed in April and July respectively were carefully examined by the veterinary surgeon who was unable to find any trace of jaundice or hepatitis. Material obtained from the slaughterings was forwarded to the department of pathology and bacteriology at the central hospital in Umeå, where the livers were found to be microscopically normal.

When considering the facts of the outbreak from the etiological point of view it must be taken into account that the

clinical picture presented in these cases can be reproduced by poisons such as phosphorus, secale and others. Vitamin deficiencies and various substances derived from decomposing material might also according to Brugsch produce jaundice. Phosphorus is used on a small scale for the purpose of killing pests, but no poisoned baits have been laid out anywhere near the sanatorium. Ergotism on such a large scale would have indicated a most unlikely flour adulteration certainly causing cases among other consumers. There has been no alteration entailing vitamin deficiency made of late in the sanatorium fare. As to Brugsch's: »Auf vermentativem Wege aus verschiedenen Nahrungsstoffen entstehenden dyspepsierzeugende und icterogene Stoffe» which are produced: »besonders in heissen Sommertagen» it is hard to see why this hypothetical poison production should have started suddenly in midwinter. Lastly, any agent of the poison group would, if administered at the same time to the entire population, have produced an absolutely simultaneous intoxication whereas instead the incidences are spread over a period of 9 weeks.

As the water supply was common to all the inhabitants I thought it advisable to have the water examined bacteriologically.

The sanatorium derives its water supply from two different sources, one being the Vindel river and the other a natural well in the sanatorium park which had been enlarged and converted into a concrete tank, sunk through the morain gravel right down to the underlying primaeval rock. The dimensions of this concrete tank is roughly  $4 \times 5 \times 1.5$  meters (see fig. 4).

Water is pumped by separate pumps from the Vindel and from the well and mixed in a high reservoir with a capacity of 180 tons, from which it is distributed by pipes to the sanatorium as well as to the scattered houses inhabited by different functionaries.

The bacteriological report showed a considerable contamination of the water  $> 240,000$  (dextros  $45^\circ$ ) and  $> 25,000$  (lactos  $37^\circ$ ) coli per liter being found in water from the reservoir and from the well, whereas water from the Vindel river was tolerably uncontaminated  $< 10$  (dextros  $45^\circ$ ) and  $< 20$  (lactos  $37^\circ$ ) coli per liter.

The obvious step of excluding the well from the water system was taken on March 14th. The 150 tons of polluted water stored in the high reservoir was, however, overlooked. As the average daily consumption is 130 tons, a rapid dilution of the contaminated



Fig. 4. The brick building in the background is the pump house erected on top of well. In bottom of opened trench the exposed sewer can be seen and its proximity to the well can be judged. (Photographer Doctor Malmqvist.)

water took place during the following days. According to a rough estimate the high reservoir contained 7 times diluted well water on the 15th, 50—60 times on the 16th and as much as 400 times on the 17th. For the purpose of argument when discussing the



Fig. 5. Close up view of corroded sewer. (Photographer Doctor Malmqvist.)

epidemiological significance of the contaminated water supply, I accordingly have chosen the 16th March as the day when the well could be considered to be excluded from the water system of the sanatorium from a practical point of view. Infrequently tapped branching pipes might have contained polluted water for several

days. To safeguard against this possibility the stored up water was ordered to be disinfected with chloride of lime on March 25th.

A sanitary inspection on the spot on March 23rd revealed that the main sewer of the sanatorium, a 9" concrete tube had been laid down in the sloping ground above the well, from which the ground water diffuses to the fountain. In its further course it is only at a distance of 4 yards from the concrete tank. It had been observed on a previous occasion 8 years ago that the concrete tubes were liable to corrosion from the outside. At that time too the well became polluted.

As no other source of contamination could be traced, it was concluded that the waste pipe must be responsible. An attempt to prove the correctness of this assumption by pouring a solution of methylene blue down one of the sinks in the sanatorium failed, however, no coloration of the water in the well being observed.

On account of the frozen ground it was impossible to expose the soil pipe at that time, but this was done late in June, when the pipes were found to be extensively corroded, both sockets and spigots falling to pieces in several places. It has not been possible to tell from the appearance of the damaged drain during what length of time the sewer might have been leaking (see fig. 5).

On February 11th 1941 the day when the first case of hepatitis occurred the population at the sanatorium of Hällnäs numbered 477 of which 342 were patients, 108 personnel and 27 family members of the different functionaries living on the premises. During the time from February 11th until March 16th when the polluted well is considered to have been excluded from the water supply 59 patients were admitted and 11 persons joined the staff, whereas the number of family members only increased by 3 persons. The total number of persons exposed to hepatitis infection transmitted by water thus is 550. A considerable but indefinite number of these individuals have of course also been exposed to infection by contact in varying degrees. During the time after March 16th when the infected water can be considered to be eliminated until June 26th, exactly one month after the falling ill of the last case in the epidemic, there has been a total immigration of 188 people of whom 156 were patients and 32 personnel. By far the greater part of the latter were locums who had to be called in to fill the vacancies caused by hepatitis among the staff of sick attendants and servants.

Out of the 550 persons referred to above 177 came down with

TABLE 3.

Number of cases of hepatitis taking ill on different dates at the Hallnäs sanatorium.  $n$  = number of cases.

Date	n	Date	n	Date	n	Date	n
11.2	1	5.3	0	27.3	4	18.4	1
12.2	1	6.3	0	28.3	3	19.4	0
13.2	0	7.3	0	29.3	12	20.4	0
14.2	3	8.3	0	30.3	7	21.4	0
15.2	0	9.3	0	31.3	8	22.4	1
16.2	5	10.3	1	1.4	8	23.4	0
17.2	5	11.3	0	2.4	7	24.4	0
18.2	2	12.3	0	3.4	5	25.4	0
19.2	2	13.3	0	4.4	3	26.4	1
20.2	3	14.3	2	5.4	6	27.4	1
21.2	1	15.3	0	6.4	1	28.4	0
22.2	2	16.3	0	7.4	6	29.4	0
23.2	0	17.3	0	8.4	4	30.4	0
24.2	1	18.3	1	9.4	5	1.5	1
25.2	3	19.3	0	10.4	2	2.5	0
26.2	0	20.3	2	11.4	1	3.5	1
27.2	0	21.3	0	12.3	4	4.5	0
28.2	1	22.3	2	13.4	1	5.5	1
1.3	0	23.3	1	14.4	6	6.5	1
2.3	1	24.3	11	15.4	5	7.5	0
3.3	0	25.3	8	16.4	0	8.5	0
4.3	0	26.3	8	17.4	0	Total	173

hepatitis during the time February 11th to May 7th. In addition one of the medical staff took ill with hepatitis on May 27th. (See table 3 and fig. 6.) — Of these 124 were patients, 45 personnel and 9 family members. Among the 188 persons who joined the sanatorium population after March 16th, when the well was excluded, no one caught hepatitis, although most of them arrived during a time when the sanatorium was literally soaked with the infection, and hepatitis cases in varying stages were distributed throughout all sections and in most of the wards and no attempts at isolation had been made. Thus 6 patients were admitted during the first week, 5 during the second week, 5 during the third week, 6 during the fourth week, 8 during the fifth week, 6 during the sixth week and 16 during the seventh week after the exclusion of the well.

Realizing the importance of this assertion great care has been taken to check the fact by going through all the case records and by taking the evidence of the medical staff. The medical

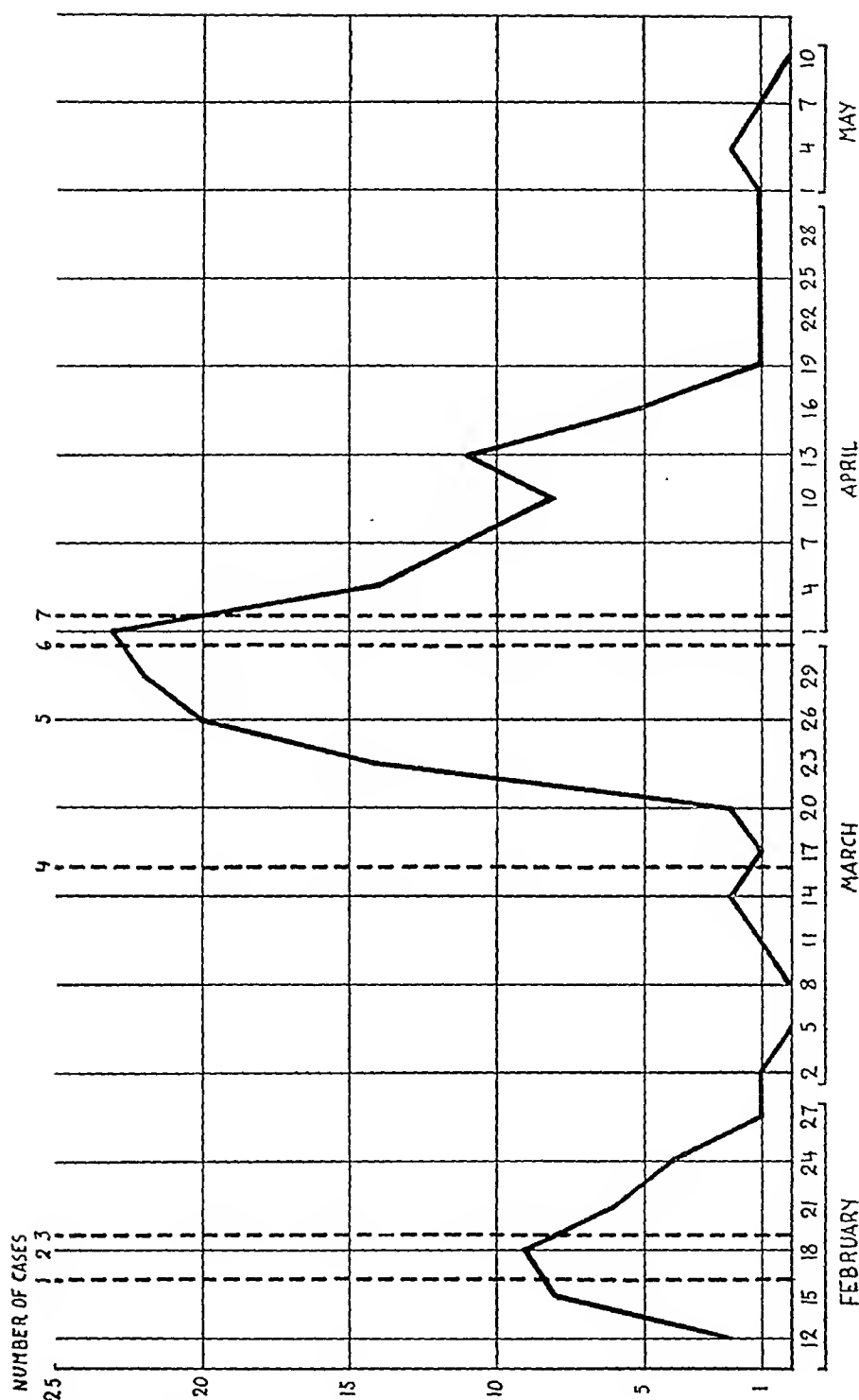


Fig. 6. Number of cases of hepatitis in the sanatorium population at Hällnäs.

1 = mode in first outbreak	= 16.20	= February 16th
2 = median " "	= 18.00	= " 18th
3 = mean " "	= $19 \pm 0.81$	= " 19th
4 = date when polluted well was excluded		= March 16th
5 = mode in second outbreak	= 26.12	= " 26th
6 = median " "	= 31.24	= " 31st
7 = mean " "	= $2.IV \pm 0.82$	= April 2nd

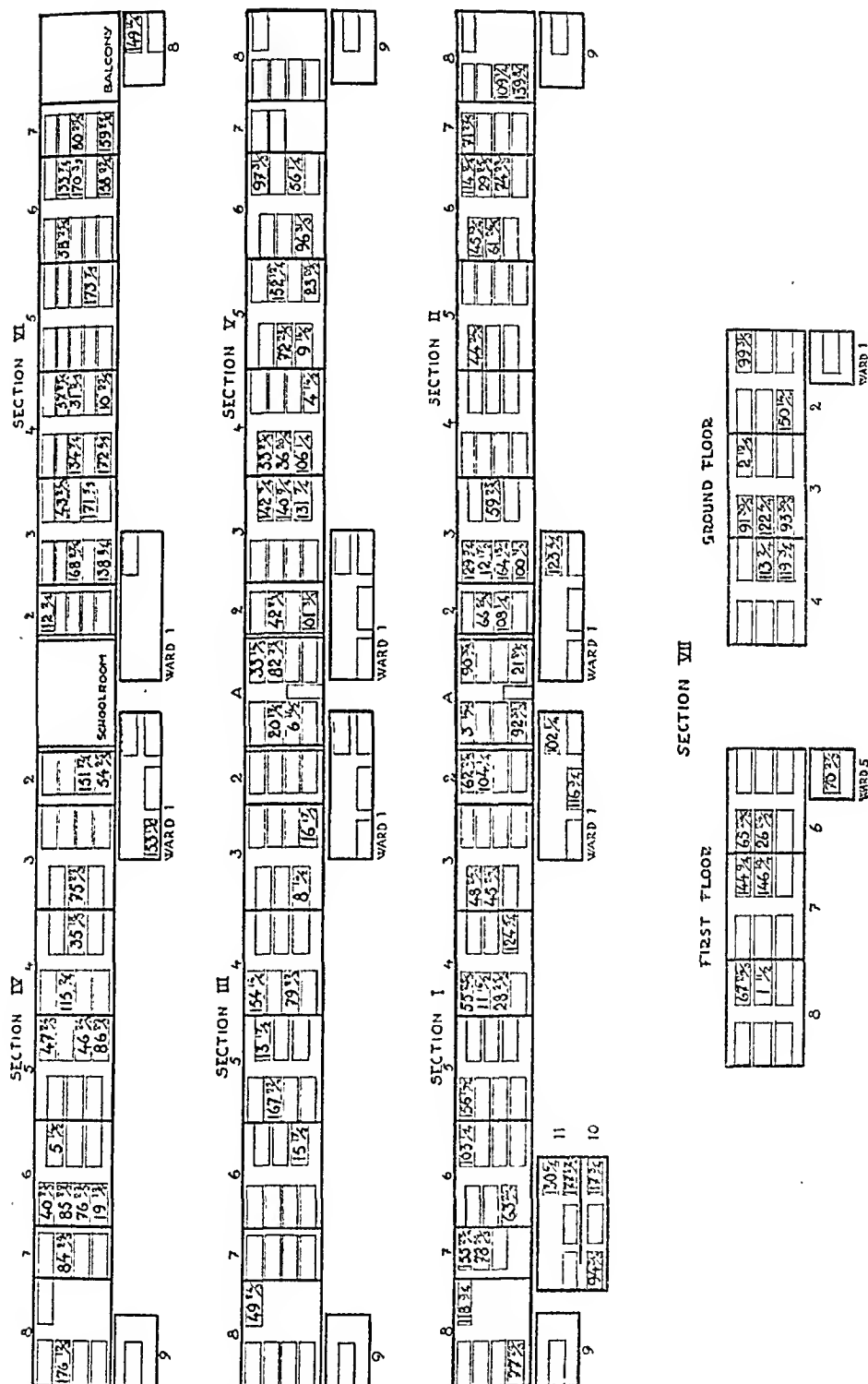


Fig. 7. Plan of sanatorium at Hällnäs with location of hepatitis cases marked by chronological numbers and dates of onset.



superintendent in a letter dated July 3rd 1942, has volunteered the following testimony:

»Only two cases of jaundice have occurred in patients admitted after March 16th. 242/41. J. K., 27 years, from Vänfors, district Vännäs. Admitted on June 7th. Had taken ill with indigestion in the middle of May, 1941. »Urine dark, jaundice one week later. Many neighbours suffering from »jaundice. As far as I know Vänfors is situated on the river Vindel. »354/41. G. D., 20 years, Karlsgård, district Sorsele. Admitted suffering »from pleurisy, on July 21st. Indigestion July 28th and 29th. Jaundice »August 2nd.»

(Transl. by author.)

The sanatorium is also the tuberculosis centre (dispensär) for roughly a third of the population of the county. Many of its frequentors have previously stayed in the sanatorium and are in the habit of going to see friends and relatives in the wards in connection with their visits.

This practice was not discouraged during the epidemic and accordingly a substantial proportion of this clientele must be considered to have been exposed to contact infection. Thus if such a mode of infection had been in operation one would expect to find some hepatitis cases in this category. A perusal of the records of all the out door patients during the first half year 1941, numbering 340, has shown that not a single one of these individuals has caught the disease.

During the first week of the epidemic 14 cases occurred simultaneously in different wards and in addition one of the nursing staff, one of the maids, one doctor's wife and one stoker went down with hepatitis. During the whole time the epidemic has continued to strike in the same arbitrary way without noticeable preference for any particular locality (see fig. 7) or category and whatever the home parish of the patient.

By far the greater number of cases had been staying for several months in the sanatorium. No evidence could be elicited either from any of those taking ill with hepatitis or from anybody admitted within the last two months before the outbreak indicating contact direct or indirectly with hepatitis cases. One exception, however, is to be noted, a patient admitted on Dec. 7th 1940 who had been working for several years at the home for the aged at Vilhelmina, where, as previously stated, a number of hepatitis cases had occurred. She had taken ill herself at the beginning of November 1940 with epigastric pains, indigestion

and vomiting lasting for more than a month. She had, however, never noticed any discolouration of skin or sclerae. During the first week of her stay in the sanatorium she was still suffering from nausea and was running a temperature. The assumption that her indigestive troubles were due to an attack of hepatitis was confirmed by the result of an analysis of citric acid and phosphatas in serum carried out on 22nd July, when these substances still were shown to be present in increased concentrations or 31.0 and 3.6 mg. respectively, values indicating lesion of the liver tissue. Considering that the patient in addition was suffering from pleursy and that this disease is known usually to depress the citric acid value, the observed titer of citric acid must be considered significant. Although not conclusively proven it might be mentioned here that her faeces were examined in connection with the general etiological investigation and that baeteriologically sterile Berkefeld filtrate from this material caused when injected into a mouse necrotic changes in the liver similar to those seen in animals inoculated with material from hepatitis cases.

Weighing the evidence provided by the Hällnäs epidemic it seems obvious that mass poisoning or intoxication as well as vitamin deficiencies must be ruled out as causative factors, and that the outbreak can only be explained by assuming infection by a specific organism. Such an assumption is perfectly compatible with all the facts and confirms the views of all previous authors on the subject except Brngsch.

The question of the nature of the contagion will be dealt with in greater detail in the concluding part of this paper. Suffice it is to mention here that the probability of a spirochaetosis icterohaemorrhagica as well as that of an infection by bacillii belonging to the typhoid, paratyphoid, Gärtner and Bang groups has been considered and that serological tests have failed to establish any connection between these microbes and actual hepatitis cases of Hällnäs.

Having decided on a specific contagion as the cause of the Hällnäs hepatitis epidemic, the question arises about the mode of infection.

Authors who have approached this subject have ventured the opinion that the disease is spread by direct contact. Thus Wallgren writes: »Das Virus verlässt den Organismus wahrscheinlich teils mit der Galle, möglicherweise auch mit dem Harn, teils mit

dem Nasenrachensekret. Das Virus wird von der letzteren Ausgangspforte auf den Rachen einer anderen Person übertragen, durchdringt die Rachenschleimhaut und führt zu einer Blutinfektion, erreicht auf dem Blutwege die Leber und greift dieses Organ an.»

Epidemiologic analysis has not permitted of any decisive conclusions regarding the time during which a case of hepatitis is infectious. Only systematic research on the infectiousness during all stages of the disease of various secreta from a sufficiently large number of cases can decide this question.

The long incubation time, however, seems to suggest a period of adaptation or multiplication of the apparently singularly hepatophile agens. The liver might eliminate the circulating virus from the hepatic or portal system or both up to a point, its parenchym becoming increasingly injured in the process. When the damage sustained reaches a certain extent the clinical symptoms of disease set in. That an accumulation of virus in the liver takes place seems exceedingly likely and the bile ought to contain it in higher concentrations than any other obtainable material.

Assuming this reasoning to be correct there is a theoretical possibility that the contagion is eliminated by the stools and urine during the time of incubation and disease. Vomited matter, however, can be expected to be particularly infectious and is most likely to be the ordinary vehicle of infection. Direct aboral transmission indicates bad hygienic habits and unsatisfactory sanitary conditions, such as can be found in overcrowded cottages where two or even three members of a family share a bed.

Under reasonably hygienic conditions, for instance those prevailing in a modern hospital or sanatorium, the infectiousness by contact should thus be expected to be limited to the period of clinical illness and in particular to the stage of vomiting.

On the face of it obviously a great portion of the cases could be explained as due to contact. From table 4 may be gathered that no less than 40 cases out of 70 could be explained as possible contacts in wards when correlated to previous cases by application of the accepted time of incubation.

In this connection the last case of the epidemic is of particular interest. As stated before the lady house physician was the last to contract the disease. She had been attending the patients throughout the epidemic and took ill on May 27th, 71 days after the closing of the well. She lived in the same flat as a colleague

and his family, sharing the bathroom and toilet facilities. This doctor's wife took ill on February 17th and the husband himself on April 22nd. Considering the long time elapsed after the elimination of the well the infection in this case can hardly have been due to contaminated water. Although having obviously been exposed to water borne infection for at least one month as well as to air borne and droplet infection for three months she escaped falling ill until the disease had actually invaded her intimate surroundings, a circumstance suggestive of an intensified exposure.

The obvious explanation of this fact, however, seems to be an altered susceptibility, a phenomenon which according to experience is of every day occurrence in various contagious diseases. The phase of non-receptivity in that case must have lasted for an appreciable length of time or at least two or three months. In this case contact infection can not be excluded.

If we turn to the table 5 we will find that there has been 54 cases of hepatitis among the personnel. If these persons had only run the same risks in the different age groups as the tubercular patients 36.6 would have caught the disease. See table 6.

The difference  $17.5 \pm 5.1$  is thus statistically proved and suggests that they should be more exposed which also has been pointed out above. The alternative idea that tuberculosis should confer a relative immunity against hepatitis virus is too fantastic to be seriously entertained. The discrepancy in morbidity between patients and personnel does not seem to provide a strong argument in favour of contact infection but indicates that contacts may be of some importance.

The following facts, however, run contrary to the conception that contact should play a conspicuous part in the spread of the disease. Thus

1) only two cases that cannot be traced to water imbibed at the sanatorium have occurred in the adjacent village of Hällnäs with separate water supply but rather lively intercourse with the sanatorium population.

2) no cases have occurred among patients or personnel arriving at the sanatorium after the exclusion of the polluted well, although their exposure to contact infection has been heavy owing to the great number of unisolated hepatitis cases in wards. Neither has any of the about 300 outdoor patients visiting the tuberculosis

TABLE 5.

Frequency of diseased persons among the patients and the personnel and their families.  $P \pm \varepsilon(P)$  = per cent of the population ( $=N$ )  $\pm$  standard error of the percentage.  $D \pm \varepsilon(D)$  = difference  $\pm$  standard error of the difference. A positive difference signifies that patients have shown higher morbidity.

		N	Hepatitis cases	$P \pm \varepsilon(P)$	$D \pm \varepsilon(D)$
Men	Patients	193	60	$31.09 \pm 3.33$	} $-8.20 \pm 9.81$
	Personnel and family members	28	11	$39.29 \pm 9.23$	
Women	Patients	208	64	$30.77 \pm 3.20$	} $-4.77 \pm 5.40$
	Personnel and family members	121	43	$35.54 \pm 4.35$	
Both sexes	Patients	401	124	$30.92 \pm 2.31$	} $-5.32 \pm 4.56$
	Personnel and family members	149	54	$36.24 \pm 3.94$	

TABLE 6.

Frequency of the disease among patients and personnel with family.  
N = number of cases.

Age in years	Patients			Personnel and family members			
				Total = n	of these hepatitis		
	N	Hepatitis	Hepatitis in % of N = a		observed number	% of n	expected number = a . n
1-5	12	1	8.33	7	1	14.29	0.58
5-10	18	5	27.78	4	1	25.00	1.11
10-15	37	15	40.54	4	2	50.00	1.62
15-20	73	30	41.10	3	3	100.00	1.23
20-25	110	47	42.73	42	25	59.52	17.95
25-30	63	14	22.22	26	8	30.77	5.78
30-35	30	7	23.33	19	7	36.84	4.43
35-40	18	1	5.56	14	5	35.71	0.78
40-45	18	4	22.22	14	2	14.29	3.11
45-50	9	—	—	1	—	—	—
50-55	10	—	—	1	—	—	—
55-60	2	—	—	10	—	—	—
60-65	1	—	—	3	—	—	—
65-70	—	—	—	1	—	—	—
Men	193	60	31.09	28	11	39.29	—
Women	208	64	30.77	121	43	35.54	—
Both sexes	401	124	30.92	149	54	36.24	—

dispensary at the sanatorium during the time of the epidemic contracted the disease.

3) finally one case of hepatitis, a conscript soldier from Vilhelmina joining the colours in Umeå, has failed to give rise to any contacts, although the soldiers are living in crowded quarters, 20 persons sharing a sleeping compartment.

A water borne infection is suggested by

1) the sudden outbreak, long domicile in sanatorium of cases and no proved contact with jaundice cases for at least three months before outbreak.

2) practically simultaneous falling ill of patients in different wards with comparatively little communication between them

medical staff

nursing staff

economy staff

engineering staff (no contact at all with patients and hardly any with the rest of the staff)

household members of staff with separate housekeeping and no *direct* contact with sanatorium population.

3) proved considerable pollution of water supply traced to the sanatorial sewer,

4) in a pig which has been given water from the polluted well and subsequently killed microscopic examination revealed necrotic and inflammatory liver changes of the type observed by Th. Andersen whereas 9 controls showed normal livers.

5) sudden cessation of epidemic on date corresponding to maximum incubation duration after date when infected water supply was excluded.

Assuming a water borne infection, the chronological distribution of cases seems to suggest that the water had been infected to a less extent at an earlier date — such as might be the case, if the suspected carrier from the home of the aged at Vilhelmina actually had been excreting the contagion during her stay at the sanatorium — and that consequently some persons have contracted the disease. They in their turn polluted the water more intensely causing a new and larger epidemic outbreak. From this point of view we should have to deal with two epidemics. If so it must be assumed that the contagion does not multiply in water and disappears after some time. As shown by the fig. 6 and table 3 representing the distribution of the cases two distinct

maximums on resp. February 18th and April 1st are discernible. The medians differ slightly from the average means indicating a certain but not very marked skew distribution. This can be explained as a skew variation of incubation times with two identical modes of infection at two different times. If so the distance between the maximums of the epidemics ought to be equal to the time of incubation. This is borne out by other observations, the distance being 42 days. (In order to determine more exactly the time when a maximum of persons took ill the modes have been computed using the following formula:  $M_0 = 3 M(D) - 2 M$ ; the corresponding dates were found to be February 16th and March 26th respectively (38 days interval).

Finally it must be kept in mind that the well was excluded on March 16th and that the last case occurred on April 19th, after which day only single cases are reported at irregular intervals until May 7th (34—52 days). This could be expected in case of a water borne infection. The time elapsed exceeds somewhat the average time of incubation. One has of course to count with time variations around maximums slightly higher than the means.

The skew distribution can be explained at least in two ways. One possibility is an initial explosive outbreak as seen in water borne infections and subsequently a smaller number of contact cases. Considering the length of the time of incubation this interpretation appears less likely, because if so, single contact cases would occur at a greater distance from the mean of the epidemic. Nor is it compatible with the fact that immigrants to the sanatorium after the date when the well was excluded did not catch the disease, although numerous hepatitis cases still were being treated. In such circumstances it remains to be assumed that the time of incubation has a skew distribution which means that the majority develop the disease after 40 days, whereas a certain number fall ill after a shorter time or approximately about 30 days and finally a few require more than 40 days for the disease to break out. Concerning these last the incubation time has been found to vary to such an extent that the distribution does not become symmetrical around the mean. This type of variation of course is reasonable, because one can always expect to come across at least single cases on the border line of susceptibility who harbour the contagion for a certain time but who only take ill when some additional morbid influence lowers their immunity.

In infectious diseases it is not unusual that the resisting power of an individual varies from time to time.

Having deduced the time of incubation and its variations from a statistical analysis of the whole epidemic it might be of interest to compare the conclusions arrived at with actual occurrences. Chance visitors to the sanatorium and other persons who have contracted the infection and subsequently developed hepatitis permit conclusions regarding the time of incubation. The following cases seem to be fairly conclusive.

1) Doctor S. E. attended a dinner party in the home of the medical superintendent of Hällnäs on March 2nd, took ill with symptoms of indigestion and high temperature on March 30th and developed jaundice on April 4th. Time of incubation 28 days.

2) Miss M. J. sister of the medical superintendent's maid who went down with hepatitis on March 26th. Acted as assistant servant at the above dinner party on March 2nd. Visited in addition her sister on March 16th. Took ill with hepatitis on April 4th. The case gives no clear information as to the time of incubation which could be either 22 or 36 days.

3) Probation nurse A. N. working at sanatorium from January 1st until March 3rd took ill on April 8th and developed jaundice on April 10th. Minimum time of incubation 36 days.

4) Mr. K. B. K. visited his mother who was staying as a patient in the sanatorium on March 8th, was served a meal during his visit at the sanatorium. He took ill on April 9th and developed jaundice on April 15th. Time of incubation 32 days.

5) Mr. S. S. H. conscript soldier from Hornsjö, Vilhelmina (visited on April 11th his cousin who shortly afterwards took ill with hepatitis), joined the regiment in Umeå on April 17th and took ill himself with hepatitis on May 13th. Incubation time 31 days.

Postulating a water borne infection the dates of admission correlated to the date when the polluted water was excluded permit of conclusions regarding the period of incubation within fairly narrow limits in the following five cases.



Chronological number	Date of admission	Date when the well was excluded	Date of onset of jaundice	Days of incubation ranging between:	
				min.	max.
154	2/3	16/3	14/4	28	43
156	7/3	»	14/4	28	38
167	14/3	»	22/4	36	38
170	15/3	»	3/5	47	48
171	15/3	»	5/5	49	50
mean: 38				—	43

The peculiar conditions encountered in the hepatitis epidemic at Hällnäs approach those usually obtained only in laboratory experiments. Factors, such as housing, diet, sanitation and water supply are uniform and easily controlled. Not only the size of the population is known but the length of its stay at the sanatorium, its previous movements and possible exposure to infection and its state of health. The exact age distribution has been ascertained. The villagers in Hällnäs and the immigrants and visitors to the sanatorium after March 16th form unimpeachable »controls».

Having proved that the contagion has been transmitted by water, the number of hepatitis cases provide a singularly reliable argument for estimating the susceptibility in this epidemic. The total morbidity works out at  $32.4 \pm 3.5$  %. Men and women are affected to the same extent, the computed difference being only  $0.39 \pm 4.07$  % (see table 7).

The conundrum presented by the significant difference in morbidity between tubercular patients and healthy inmates of the sanatorium referred to above evades attempts at explanation. The phenomenon suggests that the morbidity percentage should be considered as a minimum figure.

Considering the prevalence of the disease in different age groups it must be noted in the first place that no case has occurred in persons above 45 years of age. See table 8.

As the population numbers 38 individuals whose age exceeds this limit the conclusion might be permitted that elderly persons run a comparatively small risk of catching the disease. Middle aged persons and adolescents are particularly liable. The risk seems to be the greatest in the first decade after 20 years. That children should be particularly susceptible, as has been stated by certain authors, is not borne out, but the present

TABLE 7.

Frequency of the disease among men and women.  $P \pm \varepsilon(P)$  = per cent of the population ( $=N$ )  $\pm$  standard error of the percentage.  $D \pm \varepsilon(D)$  = difference  $\pm$  standard error of the difference. A positive difference signifies that men have shown higher morbidity.

	N	Hepatitis cases	$P \pm \varepsilon(P)$	$D \pm \varepsilon(D)$
Men	221	71	$31.13 \pm 3.14$	} $-0.39 \pm 4.07$
Women	329	107	$32.52 \pm 2.58$	

TABLE 8.

Frequency of disease in different age-groups.  $P \pm \varepsilon(P)$  = per cent of the population ( $=N$ )  $\pm$  standard error of the percentage.

Age in years	N	Hepatitis cases	$P \pm \varepsilon(P)$
1—5	19	2	$10.53 \pm 7.04$
5—10	22	6	$27.27 \pm 9.49$
10—15	41	17	$41.46 \pm 7.69$
15—20	75	33	$44.00 \pm 5.73$
20—25	153	72	$47.06 \pm 4.03$
25—30	89	22	$24.72 \pm 4.57$
30—35	49	14	$28.57 \pm 6.45$
35—40	32	6	$18.75 \pm 6.90$
40—45	32	6	$18.75 \pm 6.90$
45—50	10	—	—
50—55	11	—	—
55—60	12	—	—
60—65	4	—	—
65—70	1	—	—

material is too small to permit of certain conclusions in this respect.

### Regional cases (see map, fig. 8).

Three cases of hepatitis are known from the *village of Hällnäs*. A 25 years old man who appears to be a frequent visitor to the sanatorium and whose intimacy with a member of the staff qualifies him to be ranked as »family member» took ill on April 11th. On May 12th a servant in his house caught the disease.

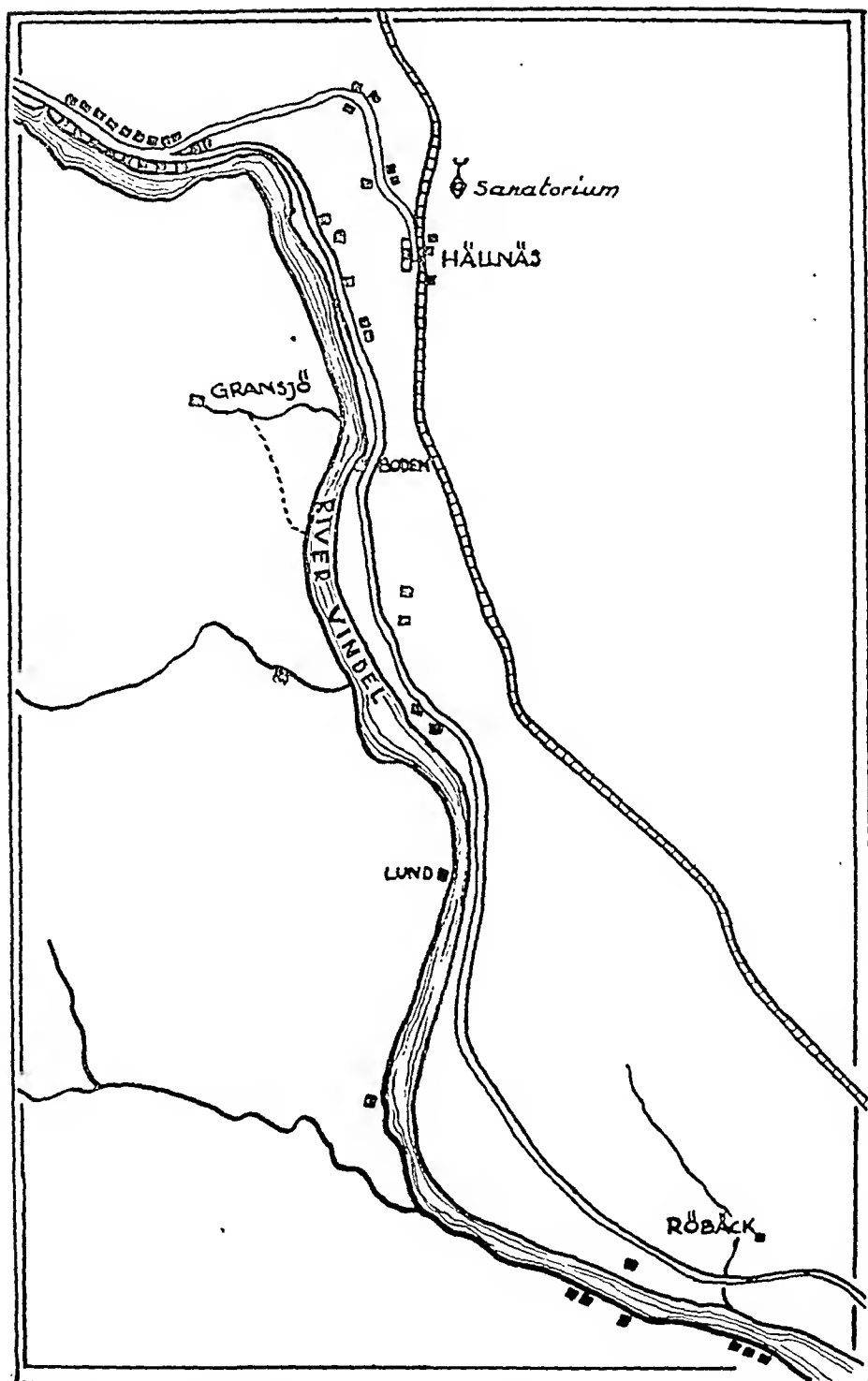


Fig. 8. Topographical map showing positions of sanatorium, the river Vindel and places where regional cases of hepatitis have occurred.

The third case occurred on May 26th when a servant employed by one of the sanatorium nurses living in the village took ill. She too probably has been visiting the sanatorium.

Presumably the first case has been infected by water, whereas the two later cases might be considered as contacts.

Two brothers in *Bodarna*, a place 2 km. south of the village of Hällnäs came down with hepatitis on April 16th and May 20th respectively. They had shared the same bed in a wood cabin when working as lumber men and parted company on April 19th (minimum incubation time 31 days). No connection with the sanatorium has been elicited.

In a house at *Gransjö* on the right hand of the Vindel river the 19 years old son had been suffering from jaundice in the middle of March. On May 4th his sister fell ill, probably infected by her brother. Questioning has failed to establish any connection with the sanatorium.

On April 8th a case of hepatitis occurred in *Röbäck*, a house on the left bank of the river Vindel, 9 km. downstream from the point where the sanatorium effluent empties into the river. Water from the river had been used for drinking. No visits had been paid to the sanatorium. Water infection seems to be likely.

A family in *Lund* living in a house 5 km. below the sanatorial effluent also had drawn their water supply from the river. During the week 8th—15th June 5 members of the household caught hepatitis. One of them had stayed for 3 days during the first week of April with one of the porters at the sanatorium whilst 3 of this family were down with hepatitis. Contact infection in this instance would postulate an incubation time of 66 days which goes against the evidence of other experiences from the sanatorium epidemic. The simultaneous outbreak strongly suggests infection by water.

A conscript soldier who returned to his home at *Rödälund*, 40 km. down the Vindel river on April 15th, took ill with hepatitis on May 13th (28 days). There has been no communication with Hällnäs or other cases. The infection might have been contracted during his stay in Umeå although no cases had occurred at the regiment. On May 26th his sister caught the disease, presumably by contact.

## Vännäs Epidemic.

As can be seen from table 1 hepatitis has been endemic in the Vännäs district during 1940 and 1941. The returns after June 30th 1941 have been as follows:

1941.						1942.							
July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Febr.	March	April	May	June	July	Aug.
7	1	8	4	7	1	4	10	23	12	38	4	3	0

Since July 8th no case. The cases occurred in the market town of Vännäs and in particular in the adjacent military camp.

In the spring of 1942 Doctor Bellander of Snrahammar fame (see chapter on literature) happened to be acting surgeon with the troops stationed in Vännäs. His attention was at once focused on the water supply. Both town and camp are served by the Vännäs water works distributing gravel filtered water from the Umeå river. An examination of the water showed considerable pollution or  $> 3000$  coli pr litre. A chlorination plant was installed on May 13th and a month later, as can be seen above, the epidemic practically came to an end. It is too early yet to tell, whether the cessation is definite, but should it prove to be so, another observation in support of water transmission will be added to the list of similar experiences from the county of Västerbotten.

## Hörnefors Epidemic.

During a visit to Hörnefors in September 1942 the author learnt that hepatitis had been widespread since the autumn 1941 in the industrial village of Hörnefors as well as in a few minor villages situated along the Hörneå river. Notification, however, had been totally neglected by the D. M. O.

A considerable time thus having elapsed since the beginning of the outbreak, it was rather difficult to find out the exact number of cases, but the following figures refer to cases which had come to the notice of the nurses and approved societies. The actual morbidity, however, certainly has been much greater.

1941.					1942.								
Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Febr.	March	April	May	June	July	Aug.	Sept.
2	14	1	1	4	5	5	1	1	3	4	2	3	6

An analysis of the outbreak reveals the usual accumulation of simultaneous cases in families. Thus 7 members of one family came down with the disease, 4 of them inside a few weeks. In another family 3 members took ill during the same month and in 6 additional families 2 cases occurred at short intervals. All the known cases can be connected with the industrial village where drinking water is drawn from a tube carrying river water for industrial purposes to the wood pulp mill. No mechanical or chemical purification is employed. Repeated bacteriological examinations have shown considerable pollution with intestinal bacteria, and the water has been pronounced unfit for consumption. By far the greater majority of the cases which it has been possible to trace have been using this water and there is more than a suspicion that the contagion has been waterborne.

### Reflections.

Of the lessons taught by the hepatitis epidemics in the county of Västerbotten that of the Hällnäs outbreak is by far the most important. The auspices presiding over the origin and development of this institutional epidemic have been singularly propitious in defining clear cut issues as well as in providing answers to many questions on which opinion for a long time has been divided.

It has been possible by analysing all possibilities to prove conclusively that the contagion in at least one epidemic of hepatitis has been transmitted by water and that other modes of infection have been negligible. The fact that the greater part of the cases if some circumstances are not taken into account could be explained as contacts on circumstantial evidence at least as strong as that usually presented in support of the airborne or droplet modes of infection invites one to increased caution in the evaluation of premises as well as in the forming of conclusions. The undeniable tendency of deducting too glibly a cause — effect connection from a time — space coincidence requires to be guarded against when judging the mechanism of infection in hepatitis.

## Clinic.

The outlines of the clinical picture in hepatitis are well known. Owing to the special circumstances presiding over the Hällnäs outbreak it has been possible to elicit very reliable and accurate dates. In particular the state of health of the patients before contracting the nosocomial disease has been recorded. It has accordingly been possible to gain a more detailed conception about the symptomatology and in particular to illuminate the initial stages of the disease which so far have escaped systematic observation.

In certain respects, however, the Hällnäs material is rather small and it has been considered desirable to complement it with the records of uncomplicated hepatitis cases, treated in the medical wards at Umeå during the years 1937—1941. In case the Hällnäs outbreak should be considered to exhibit special characteristics this complementing material might perhaps be slightly incongruous. As regards symptomatology, however, no differences exist between epidemic and sporadic hepatitis (cp. Selander) and accordingly one ought to be entitled to use the complementing dates subject to a certain amount of reservation.

### Subjective symptoms.

The clinical picture presented by the cases of epidemic hepatitis in Hällnäs is rather monotonous. In such circumstances it is hardly to be wondered at that as stated in the chapter on »Material and method» some constantly recurrent subjective complaints have not been put on record.

In 13 case histories all reference to subjective symptoms is omitted. Five additional cases (or  $3 \pm 1.3\%$ ) have run such a mild course that it has been positively stated that slight jaundice unaccompanied by any discomfort whatsoever was the only indication of the disease.

A perusal of the case records conveys the impression that the earlier cases in the epidemic suffered more severely from various

concomitant subjective symptoms than those who became the victims at the end of the epidemic. Obviously too children contracted the disease in a milder form than adults.

The correctness of these observations has been corroborated by a statistical analysis of tests to which I shall return later.

The general health of the patient is unimpaired during the time of incubation and there is no indication of imminent illness. The sudden onset is accompanied by the usual general reactions met with in different acute infectious diseases, such as headache, chills and rheumatoid pains (see table 9). Symptoms from the respiratory tract have been rare during the Hällnäs epidemic, a fact worth noting, considering the frequencies observed by Wallgren, Selander and others. In a great number of the cases abdominal pains have been complained of, localized either to the epigastric or the right hypochondric area. These pains which frequently appear to have been of considerable severity often were accompanied by pronounced tenderness over the corresponding regions. Muscular guarding was not observed. Pains and tenderness coincided with other initial symptoms and remained for two or three days only. As a rule the pains have disappeared before jaundice became manifest.

Indigestion has been the most conspicuous complaint. Initial nausea and vomiting have been noted in no less than 121 patients or  $72 \pm 3.5\%$ . The condition has as a rule lasted for several days only to subside gradually during the 1st week of the icteric stage.

The onset of hepatitis has only to a limited extent been accompanied by disturbed bowel action, constipation and diarrhoea being about equally infrequent. Later, when jaundice becomes discernible an obstinate constipation, in a few instances alternating with diarrhoea, has been observed in about 35 % of the cases.

Enlargement of the liver has been rare and was found only in the later stages of the disease.

The tabulated figure concerning how often the hepatitis patients have been complaining of itch, gives a false impression of the frequency of this phenomenon. On being approached the house physicians have admitted that a far greater number than the figures would imply have been afflicted by this discomfort. In such circumstances the figure given thus has no significance.



TABLE 9.

Frequency of different symptoms in 166 cases of hepatitis expressed in percentage

$P \pm \varepsilon(P)$  = per cent  $\pm$  standard error of the percentage.

Symptoms	Initial		During the disease	
	Number	$P \pm \varepsilon(P)$	Number	$P \pm \varepsilon(P)$
Total number of patients observed	166	—	—	—
Headache	27	$16.3 \pm 2.9$	3	$1.8 \pm 1.0$
Rigor	14	$8.4 \pm 2.2$	—	—
Rheumatoid pains (total)	30	$18.1 \pm 3.0$	—	—
» » in muscles	22	$13.3 \pm 2.6$	3	$1.8 \pm 1.0$
» » » joints	8	$4.8 \pm 1.7$	—	—
Angina, pharyngitis and coryza	6	$3.6 \pm 1.4$	—	—
Nausea	38	$22.9 \pm 3.3$	31	$18.7 \pm 3.0$
Vomiting	83	$50.0 \pm 3.9$	70	$42.2 \pm 3.8$
Constipation	10	$6.0 \pm 1.9$	54	$32.5 \pm 3.6$
» alternating with diarrhoea	—	—	4	$2.4 \pm 1.2$
Diarrhoea	7	$4.2 \pm 1.6$	6	$3.6 \pm 1.4$
Abdominal pains (total)	61	$36.8 \pm 3.7$	—	—
» » (epigastric)	56	$33.7 \pm 3.7$	—	—
» » (in liver region)	5	$3.0 \pm 1.3$	—	—
Palpable enlargement of liver	—	—	8	$4.8 \pm 1.7$
Anorexia	—	—	12	$7.2 \pm 2.0$
Itching	—	—	12	$7.2 \pm 2.0$
Epistaxis	1	—	—	—

### Duration of stay in bed.

In the first place it is interesting to see during what length of time the jaundice cases have had to be confined to bed. When investigating this matter naturally only those cases can be considered who previously have spent a greater or smaller part of the day out of bed.

Even though the time in bed in patients suffering from tuberculosis where rest cures in bed form an integral part of the regime must not be considered as representing normal conditions when healthy persons succumb to jaundice, the figures obviously are of some interest.

On an average the cases have been confined to bed during  $28.8 \pm 1.2$  days. The first 53 cases have stayed in bed during  $30.7 \pm 1.6$  days, whereas the following 54 cases have been confined to bed  $26.9 \pm 1.7$  days.

The difference  $3.8 \pm 2.3$  is not statistically significant or probable. The periods in bed do not provide evidence of a change in the characteristics of the disease during the course of the epidemic. In any case there is no sign of increased severity.

However, it must be borne in mind that the material has been subjected to selection as permanently bedridden patients have been excluded and consequently long periods of bed treatment might have been withdrawn from the material.

Anyhow, in this as in other diseases one has to count with skew distribution where patients treated with prolonged stays in bed increase the average figures. In order to find out if this is the case one has to calculate the median. On having done so it turns out that the median is slightly less than the mean. In the total material the median is found to be 26 days or 2.8 days less than the mean. This shows that the distribution is not very skew. Owing to chance one has to expect some slight difference between median and mean. The same difference between medians and means is found in the first 53 and the later 54 cases which of course was to be expected. Furthermore the median in the first group works out at 21 days, in the second at 25 days, the difference not being of a magnitude to permit conclusions regarding changes in the severity of the disease during the course of the epidemic.

### Preicteric stage.

The length of the preicteric stage has never been properly ascertained because cases with exact observations on the occasionally slight but at other times more severe symptoms during the interval between the initial illness and the appearance of jaundice have been lacking.

In the present material where the patients have been constantly watched, the dates of the initial illness were carefully noted and checked against the temperature graphs. The first appearance of jaundice too has been meticulously registered and verified by the Meulengraecht test.

Combining these observations the preicteric stage in the present material is found to last 5.9, i. e. practically 6 days. The standard deviation is 2.82 or approximately 3 days which means that the period occasionally is curtailed to an odd day or two whilst it on the other hand exceptionally might extend to more

than a fortnight. The distribution is somewhat skew. It is of particular interest to investigate whether the length of the preicteric period varies in the course of the epidemic.

TABLE 10.

Duration of preicteric stage in days. I = the first 81 cases. II = the later 80 cases. Mean  $\pm$  standard error for I =  $6.52 \pm 0.31$ , for II =  $5.21 \pm 0.30$ , for I + II =  $5.87 \pm 0.22$ . Standard deviation for I =  $\pm 2.80$  for II =  $\pm 2.68$  for I + II =  $\pm 2.82$ .

Days	Number of cases		
	I	II	I + II
0	—	1	1
1	2	5	7
2	4	11	15
3	4	3	7
4	11	11	22
5	7	13	20
6	15	12	27
7	9	8	17
8	11	9	20
9	8	4	12
10	6	1	7
11	—	1	1
12	2	—	2
13	—	—	—
14	1	—	1
15	—	1	1
16	1	—	1
Total	81	80	161

For practical reasons and considering that one is used to expect an increased virulence in the course of an epidemic the material has been divided up into two parts one containing the earlier, the other the later half of the cases. It now turns out that the preicteric stage is longer in those cases who fell ill during the later period. The difference, being  $1.3 \pm 0.43$  is statistically significant and justifies the conclusion that the preicteric stage was shorter in the beginning of the epidemic.

This is interesting considering that the temperature too will be shown later on to be higher in the beginning of the epidemic than towards its end.

It appears natural to assume that in cases running a higher temperature jaundice is liable to develop more quickly.

As the figures must be considered as sufficiently conclusive no computation of the correlation between the initial rise of temperature and the length of preicteric stage has been carried out.

### Weights.

In tubercular subjects the *weights* cannot be expected to remain constant for longer periods. Some individuals lose weight on account of the consumptive disease, while others put on weight owing to the diet. What the result would turn out to be in a material observed during an extended span of time cannot be estimated off hand.

When dealing with short periods, however, pronounced weight fluctuations are not to be expected, but the weight may be considered to be constant. If an acute infection is superimposed in a material of this kind, the consequence ought to be a loss of average weight, partly on account of loss of fluid through vomiting and the like.

Following this trend of thought the alteration in weights has been computed in different persons. Starting from weight figures before and at a safe distance from the hepatitis infection, the amounts of loss or gain respectively have been calculated. The preceding weighings, however, have been made at varying time intervals which is accounted for by the impossibility to anticipate the date when the patient would contract hepatitis.

According to our calculations the patients had last been weighed on an average 12 days before taking ill, but the variations are considerable and extend upwards as far as a month.

Subsequently average differences have been computed between the weights of departure and those observed during hepatitis. Referring to the figure corresponding to the tenth day before onset of the illness it may be seen that the weight remains constant during some time prior to this date.

Following the falling ill a loss of weight sets in which becomes obvious after about 2 weeks and then gradually diminishes during the following 2 or 3 weeks to become compensated after slightly more than a month. See fig. 9 and tables 11, 12 and 13.

To judge by weight figures the duration of the illness would be a little more than a month. Putting on weight ought to indicate recovery. A comparison between earlier and later cases does not indicate differences of interest but the figures concerning this analysis have been included for the sake of completeness.

TABLE 11.

Differences in weights and suspension stability of the erythrocytes between different days in the disease and the time before taking ill in the whole material.  $n$  = number observations.  $M \pm r(M)$  = mean  $\pm$  standard error of the mean.

Days	Differences in weights		Differences in suspension stability readings	
	$n$	$M \pm r(M)$	$n$	$M \pm r(M)$
- 24-- - 19	2	+ 0.15	2	+ 1.00
- 18-- - 13	3	+ 0.47	6	+ 0.83
- 12-- - 7	17	+ 0.024 $\pm$ 0.284	6	- 2.83
- 6-- - 1	27	+ 0.11 $\pm$ 0.17	18	- 2.9 $\pm$ 2.3
0--5	30	- 0.35 $\pm$ 0.18	31	- 4.2 $\pm$ 2.7
6--11	37	- 0.98 $\pm$ 0.28	36	+ 3.5 $\pm$ 3.0
12--17	39	- 1.74 $\pm$ 0.23	26	+ 11.9 $\pm$ 4.9
18--23	49	- 1.58 $\pm$ 0.28	33	+ 11.9 $\pm$ 2.3
24--29	37	- 1.72 $\pm$ 0.32	29	+ 13.1 $\pm$ 2.9
30--35	46	- 1.13 $\pm$ 0.34	30	+ 8.5 $\pm$ 4.1
36--41	33	- 0.50 $\pm$ 0.42	34	+ 6.5 $\pm$ 2.5
42--47	46	- 0.12 $\pm$ 0.33	32	+ 4.3 $\pm$ 3.1
48--53	36	- 0.86 $\pm$ 0.45	32	+ 1.8 $\pm$ 3.0
54--59	19	- 0.35 $\pm$ 0.65	22	+ 0.59 $\pm$ 5.12
60--65	36	- 0.27 $\pm$ 0.50	23	+ 5.7 $\pm$ 3.1
66--71	24	- 1.29 $\pm$ 0.61	20	+ 2.0 $\pm$ 4.9
72--77	20	- 0.18 $\pm$ 0.76	15	- 4.5 $\pm$ 4.8
78--83	27	- 0.26 $\pm$ 0.58	21	+ 3.6 $\pm$ 2.3
84--89	13	- 2.02	5	+ 3.0
90--95	5	- 1.04	3	+ 17.0
96--101	2	+ 0.4	5	+ 9.6
102--107	1	+ 6.8	1	- 3.0
108--113	1	- 2.1	1	+ 13.0
114--119	1	- 2.7	1	- 2.0

## Temperature.

Temperature is another general symptom of interest. Working on noon temperatures a collocation shows figures a little above 37° C during the days immediately before falling ill. On the latter date the temperature rises to 38.3° C which of course could be expected as the time of falling ill largely has been determined by the onset of fever. Temperature attains its maximum during the first days of illness then drops slightly during the first week but remains raised a little until about the third week when normal values are again reached. The beginning of jaundice is not accompanied by a rise of temperature.

As only graphs from afebrile patients and personnel could be

TABLE 12.

Differences in weights and suspension stability of the erythrocytes between different days in the disease and the time before taking ill in a group consisting of 57 patients who contracted hepatitis during the earlier half

of the epidemic = group I.  $n$  = number of observations,

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days	Differences in weights		Differences in suspension stability readings	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
— 24— — 19	1	0	—	—
— 18— — 13	—	—	1	+ 26
— 12— — 7	5	— 0.04	1	+ 13
— 6— — 1	9	— 0.02	5	— 3.8
0—5	11	— 0.35 $\pm$ 0.23	16	— 4.3 $\pm$ 2.9
6—11	22	— 0.97 $\pm$ 0.26	20	— 0.55 $\pm$ 4.52
12—17	11	— 2.06 $\pm$ 0.41	13	+ 19.5 $\pm$ 7.9
18—23	28	— 1.91 $\pm$ 0.27	13	+ 16.2 $\pm$ 2.5
24—29	17	— 1.95 $\pm$ 0.45	19	+ 11.6 $\pm$ 3.1
30—35	19	— 1.55 $\pm$ 0.49	12	+ 11.8 $\pm$ 8.4
36—41	21	— 1.07 $\pm$ 0.42	18	+ 11.7 $\pm$ 4.1
42—47	18	— 0.52 $\pm$ 0.49	17	+ 6.4 $\pm$ 4.3
48—53	29	— 0.82 $\pm$ 0.45	17	+ 1.1 $\pm$ 4.7
54—59	5	— 1.34	12	+ 6.3 $\pm$ 7.6
60—65	18	— 0.27 $\pm$ 0.72	12	+ 10.1 $\pm$ 3.8
66—71	15	— 2.42 $\pm$ 0.49	14	+ 0.14 $\pm$ 6.31
72—77	9	— 1.50	9	— 1.22
78—83	20	— 0.25 $\pm$ 0.70	15	+ 6.1 $\pm$ 2.9
84—89	11	— 1.7 $\pm$ 1.0	5	+ 3
90—95	5	— 1.04	3	+ 17
96—101	2	+ 0.40	4	+ 12.3
102—107	1	+ 6.8	1	— 3
108—113	1	— 2.1	1	+ 13
114—119	1	— 2.7	—	—

used the material worked on does not include all the hepatitis cases but it is large enough to convey a fair idea of the trend.

Whether consumptives and healthy persons react with fever in the same way can be discussed. It is always possible to maintain that tubercular subjects are more liable to become feverish. There is, however, hardly reason to believe that such factors would be of greater importance. Anyhow, the figures quoted reflect to a certain extent the relative displacement of temperature during the illness. Here also a comparison has been made between early and late cases in the epidemic. This shows the period of initial fever to be more pronounced in the beginning of the outbreak. Fundamentally it might have been convenient

TABLE 13.

Differences in weights and suspension stability of the erythrocytes between different days in the disease and the time before taking ill in a group consisting of 56 patients who contracted hepatitis during the later half of the epidemic = group II.  $n$  = number of observations.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days	Differences in weights		Differences in suspension stability readings	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
— 24— — 19	1	+ 0.30	2	+ 1.0
— 18— — 13	3	+ 0.47	5	— 4.2
— 12— — 7	12	+ 0.05 $\pm$ 0.33	5	— 6.0
— 6— — 1	18	+ 0.18 $\pm$ 0.21	13	— 2.6 $\pm$ 1.9
0—5	19	— 0.36 $\pm$ 0.25	15	— 4.1 $\pm$ 4.7
6—11	15	— 1.00 $\pm$ 0.59	16	+ 8.6 $\pm$ 3.4
12—17	28	— 1.61 $\pm$ 0.28	13	+ 4.4 $\pm$ 5.3
18—23	21	— 1.13 $\pm$ 0.53	20	+ 9.2 $\pm$ 3.3
24—29	20	— 1.53 $\pm$ 0.47	10	+ 15.9 $\pm$ 6.2
30—35	27	— 0.83 $\pm$ 0.47	18	+ 6.3 $\pm$ 4.0
36—41	12	+ 0.50 $\pm$ 0.83	16	+ 0.56 $\pm$ 2.09
42—47	28	+ 0.14 $\pm$ 0.44	15	+ 1.8 $\pm$ 4.7
48—53	7	— 1.01	15	+ 2.6 $\pm$ 3.8
54—59	14	+ 0.0071 $\pm$ 0.7311	10	— 6.3 $\pm$ 6.2
60—65	18	— 0.27 $\pm$ 0.70	11	+ 0.82 $\pm$ 4.58
66—71	9	+ 0.60	6	+ 6.17
72—77	11	+ 0.91 $\pm$ 1.07	6	— 9.50
78—83	7	— 0.29	6	— 2.67
84—89	2	— 3.70	—	—
90—95	—	—	—	—
96—101	—	—	1	— 1
102—107	—	—	—	—
108—113	—	—	—	—
114—119	—	—	1	— 2.0

to split the material between the two distinct epidemics, but as the number of cases in the first outbreak is too small to admit of conclusions, the material has been divided into two equal groups on account of statistical consideration, the standard errors becoming smaller that way.

The computed differences are found to be significant during the first three days of the illness. Accordingly there can be no doubt that the fever is more pronounced in the earlier cases. As a rule epidemics are considered to become more malignant as the time passes. This has been explained as being due to an increased virulence of the contagion brought about by repeated passages

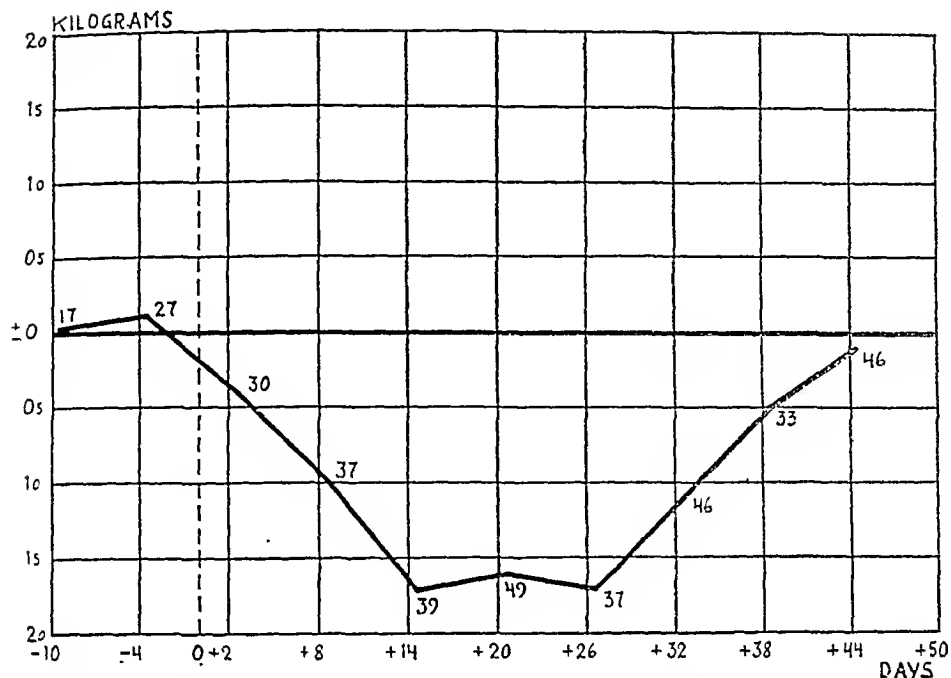


Fig. 9. Average loss in weights at 6 days intervals after falling ill in 113 sanatorium patients suffering from hepatitis.

through successive hosts. On this occasion the development apparently has been in the opposite direction. Accordingly it only remains to explain the observed displacement by assuming that in the beginning of this as in other epidemics those most susceptible might possibly contract the disease first and accordingly develop more pronounced symptoms. See fig. 10 and table 14.

### Suspension stability of the erythrocytes.

Alterations in the suspension stability of the erythrocytes reflect a general reaction much in the same way as do changes of temperature and thus are worthy of attention. The material used is formed by tested tubercular patients and no selection has been made. Thus it is to be expected that the suspension stability is more or less lowered already before their falling ill with hepatitis. Accordingly in this calculation the differences from the last values available before the onset of hepatitis have been computed.

If it had been possible to tell in advance if and when a person would contract hepatitis the suspension stability could have been tested at exactly the same date in all cases. In reality, however, the date must vary, and on an average the value of departure



TABLE 14.

Means of noon temperatures in the earlier (group I) as well as in the later (group II) groups of each 62 cases.  $n$  = number of observations.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days	Group I		Group II		Groups I + II	
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$
— 5	—	—	1	38.5	1	38.5
— 4	1	37.6	1	38.0	2	38.8
— 3	2	37.3	2	37.3	4	37.3
— 2	6	37.2	9	37.4	15	37.320 $\pm$ 0.084
— 1	42	37.060 $\pm$ 0.040	39	37.126 $\pm$ 0.048	81	37.091 $\pm$ 0.031
0	50	38.17 $\pm$ 0.11	57	38.18 $\pm$ 0.12	107	38.175 $\pm$ 0.080
1	55	38.73 $\pm$ 0.11	60	38.12 $\pm$ 0.11	115	38.410 $\pm$ 0.083
2	56	38.36 $\pm$ 0.13	60	37.81 $\pm$ 0.11	116	38.078 $\pm$ 0.090
3	57	38.18 $\pm$ 0.12	60	37.72 $\pm$ 0.12	117	37.941 $\pm$ 0.081
4	59	37.95 $\pm$ 0.11	61	37.674 $\pm$ 0.095	120	37.811 $\pm$ 0.073
5	60	37.78 $\pm$ 0.10	62	37.526 $\pm$ 0.072	122	37.649 $\pm$ 0.062
6	61	37.584 $\pm$ 0.081	59	37.470 $\pm$ 0.071	120	37.526 $\pm$ 0.055
7	53	37.668 $\pm$ 0.092	58	37.521 $\pm$ 0.084	111	37.591 $\pm$ 0.062
8	46	37.78 $\pm$ 0.28	54	37.480 $\pm$ 0.073	100	37.594 $\pm$ 0.058
9	44	37.711 $\pm$ 0.089	49	37.418 $\pm$ 0.061	93	37.557 $\pm$ 0.054
10	38	37.724 $\pm$ 0.086	45	37.358 $\pm$ 0.069	83	37.525 $\pm$ 0.057
11	30	37.82 $\pm$ 0.11	38	37.329 $\pm$ 0.079	68	37.544 $\pm$ 0.071
12	23	37.68 $\pm$ 0.10	27	37.326 $\pm$ 0.078	50	37.488 $\pm$ 0.067
13	18	37.60 $\pm$ 0.10	14	37.46 $\pm$ 0.10	32	37.540 $\pm$ 0.072
14	13	37.75 $\pm$ 0.16	10	37.54 $\pm$ 0.15	23	37.66 $\pm$ 0.13
15	9	37.63	10	37.46 $\pm$ 0.15	19	37.51 $\pm$ 0.11
16	10	37.60 $\pm$ 0.20	4	37.53	14	37.58 $\pm$ 0.14
17	6	37.50	5	37.60	11	37.55 $\pm$ 0.071
18	5	37.28	4	37.48	9	37.37
19	4	37.33	3	37.50	7	37.40
20	3	37.37	2	37.30	5	37.34
21	2	37.55	1	37.30	3	37.47
22	2	37.85	—	—	2	37.85
23	1	38.0	—	—	1	38.0
24	1	37.9	—	—	1	37.9
25	1	39.0	—	—	1	39.0
26	1	39.0	—	—	1	39.0
27	1	37.9	—	—	1	37.9
28	1	37.1	—	—	1	37.1

corresponds to the 16th day with variations between 24 and 0 days before the onset.

By inspection of fig. 11 and tables 11, 12 and 13 will be gathered that the suspension stability becomes lowered, when the patient falls ill, the displacement appearing after about one or two weeks. A maximum decrease is reached after about 4 weeks and about 40 days later normal conditions seem to be reestab-

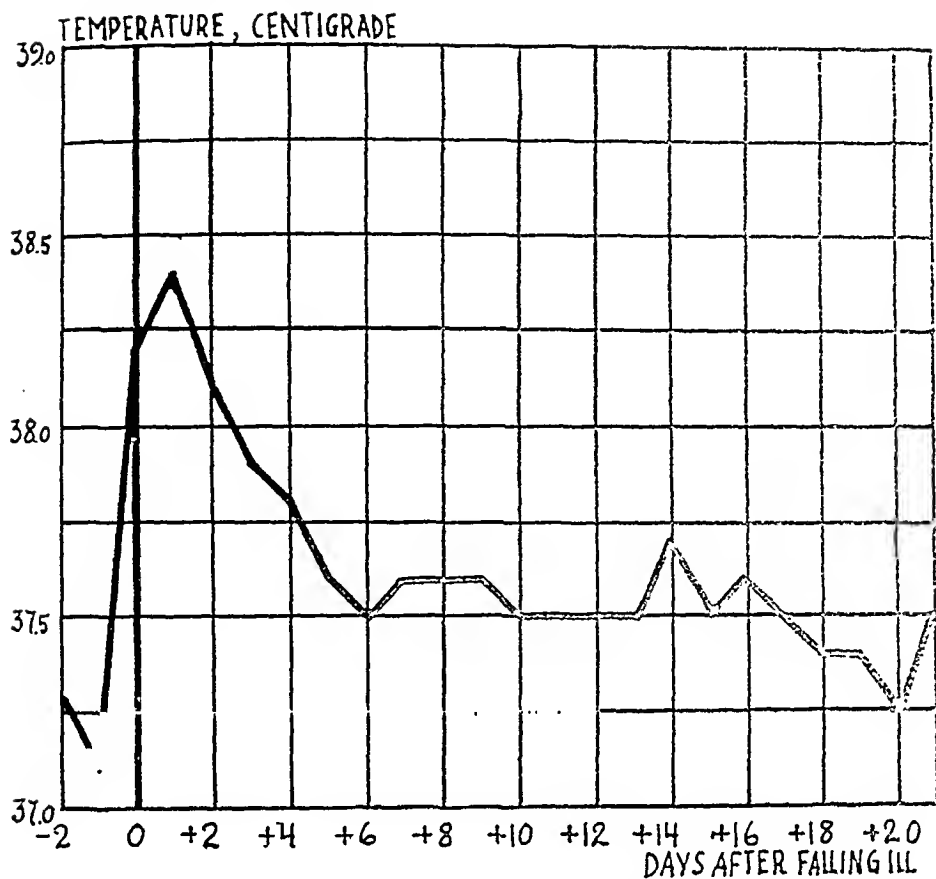


Fig. 10. Average temperature before and after the disease in 124 hepatitis cases of the Hällnäs material. 0 is the day when the disease began.

lished. A marked difference between early and late cases cannot be shown, which might be accounted for by the fact that the tests have not been carried out regularly and that the material consequently is too small to give significant differences.

In tables 15 and 16 are given the figures computed from the cases treated in the Umeå hospital together with the corresponding figures from the sanatorium material similarly arranged. In both instances figures are given for the difference between the first 6 days and later days. We find in both materials a lowering of the suspension stability and this disturbance seems to last at least two months. Cp. fig. 12. For the hospital patients the differences are smaller during the end of the first month than for the sanatorium cases which might be explained as a result of a tendency to lower suspension stability because of tuberculosis.

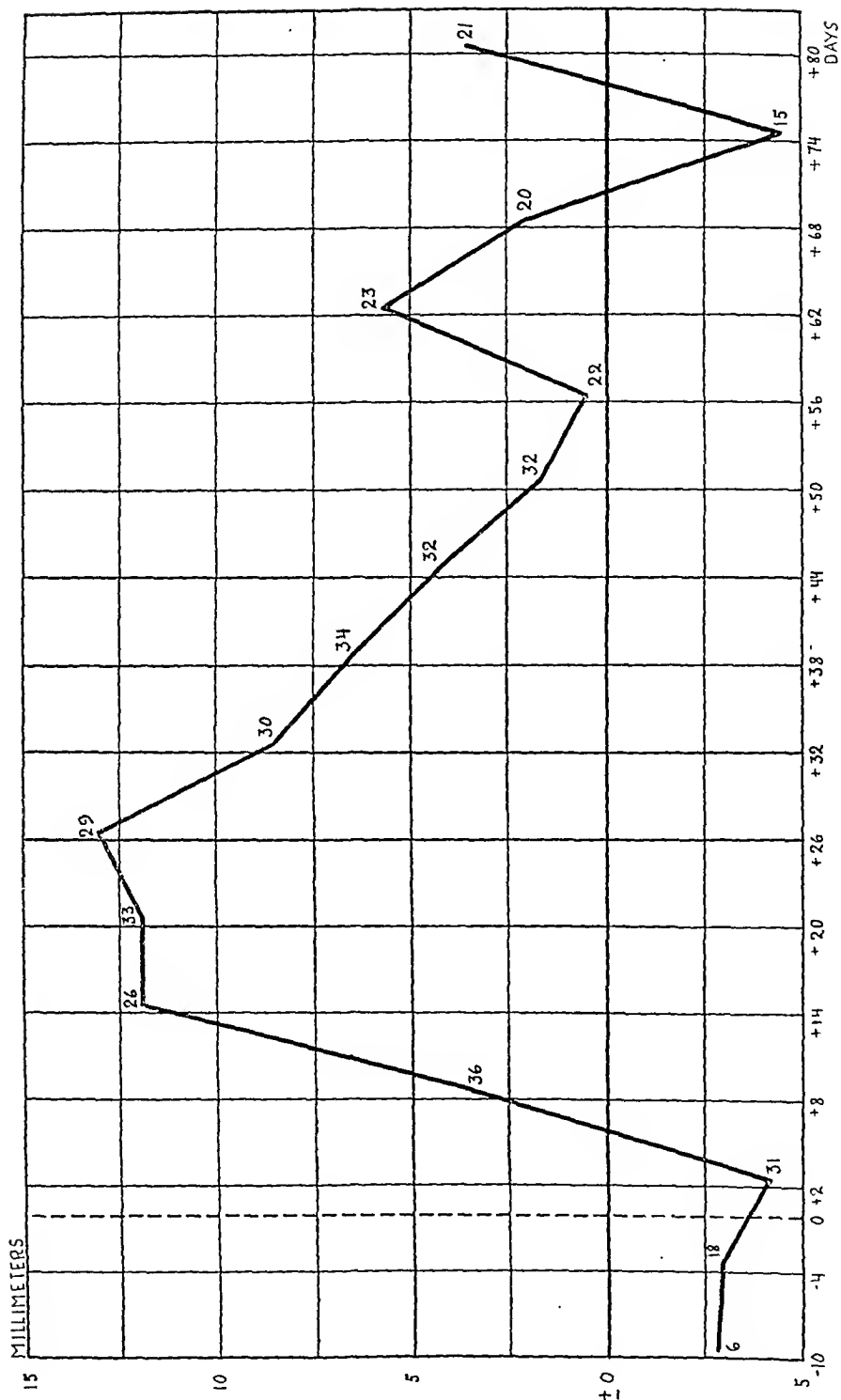


Fig. 11. Average decrease in the suspension stability of the erythrocytes after falling ill at 6 days intervals in 113 sanatorium patients suffering from hepatitis.

TABLE 15.

Mean of the suspension stability = S. R. on different times after taking ill expressed in millimeters in 149 cases of uncomplicated hepatitis treated at the Umeå hospital.  $n$  = number of cases.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after falling ill	S. R.	
	$n$	$M \pm \varepsilon(M)$
0—5	38	$11.3 \pm 1.4$
6—11	108	$16.9 \pm 1.4$
12—17	97	$18.1 \pm 1.4$
18—23	89	$20.3 \pm 1.6$
24—29	82	$18.5 \pm 1.4$
30—35	56	$16.7 \pm 1.9$
36—41	36	$21.0 \pm 3.1$
42—47	23	$17.0 \pm 3.3$
48—53	16	$22.8 \pm 4.5$
54—59	11	$19.4 \pm 6.1$

TABLE 16.

Differences between figures for the mean suspension stability for the first 6 days and later days in 113 sanatorium and 149 hospital cases of hepatitis.  $n$  = number of observations.  $D \pm \varepsilon(D)$  = difference  $\pm$  standard error of the difference.

Days after onset of illness	Differences in suspension stability			
	Hospital		Sanatorium	
	$n$	$D \pm \varepsilon(D)$	$n$	$D \pm \varepsilon(D)$
7—11	146	$+ 5.6 \pm 2.0$	67	$+ 7.7 \pm 4.0$
12—23	186	$+ 7.8 \pm 1.8$	59	$+ 16.1 \pm 3.8$
24—35	138	$+ 6.5 \pm 1.7$	59	$+ 15.0 \pm 3.7$
36—47	59	$+ 8.1 \pm 2.7$	66	$+ 9.6 \pm 3.4$
48—59	27	$+ 10.1 \pm 4.0$	54	$+ 5.5 \pm 3.4$
60—89	21	$+ 8.0 \pm 2.6$	84	$+ 6.5 \pm 2.9$

### The Meulengracht test.

In the literature as a rule the figures below 8 seem to be considered to be normal in the Meulengracht test. However, no investigation seems to have been made into the distribution of

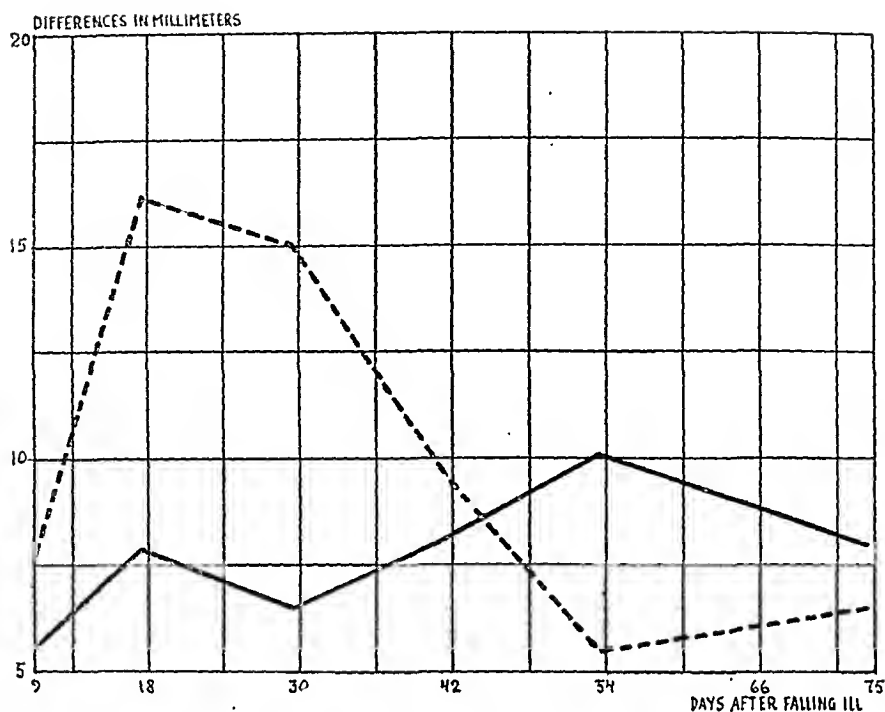


Fig. 12. Changes in suspension stability of the erythrocytes in 113 hepatitis cases at the sanatorium of Hällnäs (dotted line ..) and 149 uncomplicated hepatitis cases treated at the Umeå hospital (drawn line ..).

figures in healthy persons. Consequently the figure mentioned above is not very reliable and therefore a special investigation into this question has been made. Healthy persons have been tested simultaneously by two laboratory assistants A. and K. H. There is no proved difference between the results arrived at by these mutually independent workers, the actual figure being  $0.08 \pm 0.05$ . The agreement in fact is as good as could be desired. It must be admitted, however, considering that only two investigators were employed, that such good an agreement is not always to be expected. My two assistants presumably have been working in a more similar way than could be expected by workers in different laboratories. As a whole, however, the figure arrived at shows that subjective factors hardly play too important a part, because if so such a close agreement would hardly have been reached.

Regarding the reliability of any particular observation, a standard error of  $\frac{1}{2}$  unit (0.51) must be accounted for which means that any particular value might vary by a maximum of

1½ units upwards or downwards. Expressed in percentage the standard error was found to be 6.8 %. The method thus can be considered to be reasonably exact.

In order to gain some idea about the normal value and its variation, the mean, standard deviation and distribution have been computed in a material of 270 readings made inside 24 hours.

The mean was found to be  $7.53 \pm 0.14$ . The standard deviation is 2.12 and accordingly the normal variation is limited by 1.2 and 13.9 respectively. The distribution, however, is slightly skew which might be found by inspection of the diagram, fig. 13.

How the Meulengracht test figures are affected when the blood samples are kept stored has been investigated by retesting after 48, 72, 96 and 120 hours. It then becomes apparent that on an average the values rise after 4 to 5 days by about 3 units.

The difference between the readings after 24 and 120 hours is  $2.95 \pm 0.57$ . The distribution is slightly skew all the time and in samples that have been kept for 120 hours the variation ranges between 2 and 20. See tables 17 and 18 and fig. 13.

TABLE 17.

Distribution of Meulengracht readings at 24 hours intervals after taking the blood test:

Meulengracht figures	Number of tests in hours				
	24	48	72	96	120
4	9	1	1	1	1
5	21	6	5	1	} 2
6	47	14	6	3	
7	64	23	10	9	} 9
8	40	33	25	15	
9	25	45	27	16	} 12
10	12	23	19	16	
11	6	17	18	7	} 9
12	7	7	16	13	
13	1	5	8	9	} 2
14	5	4	3	8	
15	2	5	4	3	} 2
16	—	—	3	2	
17	—	1	—	3	} 2
18	—	—	—	—	
19	—	—	—	—	1
Total	239	184	145	106	41

TABLE 18.

Average figures for Meulengracht tests and skewness of the distribution in normal persons at 24 hours intervals after taking the blood test.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.  $\sigma$  = standard deviation.

$S_L \pm \varepsilon(S_L)$  = skewness according to Lindeberg  $\pm$  standard error.

Interval in hours	Number of cases	$M \pm \varepsilon(M)$	$\sigma$	$S_L \pm \varepsilon(S_L)$
24	239	$7.53 \pm 0.14$	2.12	— $9.00 \pm 1.94$
48	184	$9.03 \pm 0.17$	2.27	— $16.30 \pm 2.21$
72	145	$9.74 \pm 0.20$	2.45	— $1.03 \pm 2.49$
96	106	$10.42 \pm 0.27$	2.76	— $7.55 \pm 2.91$
120	41	$10.48 \pm 0.55$	3.52	— $8.54 \pm 4.69$

24 hours.

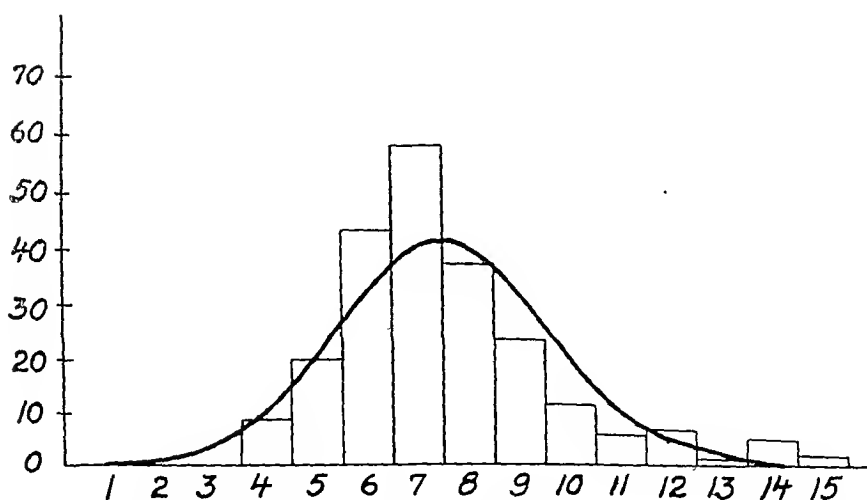


Fig. 13. Observed distribution of Meulengracht values in healthy persons and a normal curve smoothed to the observed frequencies.

When comparing the values obtained in healthy persons with those found in hepatitis cases, the latter are found to rise coinciding with or shortly before the onset of jaundice. During the first weeks the values remain high, then drop slowly towards

normal. Normal figures have, however, not yet been reached within on an average two months. See table 19 and fig. 14.

TABLE 19.

Average of Meulengracht tests and the standard deviations in the whole hepatitis material at Hällnäs (166 cases).  $N$  = number of observations.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error of the mean.  $\sigma$  = standard deviation.

Days	N	$M \pm \epsilon(M)$	$\sigma$
— 4 — — 2	12	$9.08 \pm 0.99$	3.42
— 1 — 1	70	$26.8 \pm 1.5$	12.7
2 — 4	52	$35.7 \pm 2.7$	19.8
5 — 7	24	$25.8 \pm 4.1$	20.3
8 — 10	34	$19.4 \pm 2.6$	15.2
11 — 13	50	$16.2 \pm 2.2$	15.5
14 — 16	58	$14.1 \pm 1.5$	11.7
17 — 19	49	$15.6 \pm 2.5$	17.6
20 — 22	36	$13.8 \pm 1.6$	9.6
23 — 25	29	$12.38 \pm 0.70$	3.76
26 — 28	31	$13.4 \pm 1.2$	6.8
29 — 31	16	$12.1 \pm 1.5$	6.2
32 — 34	28	$11.04 \pm 0.98$	5.19
35 — 37	6	10.83	.
38 — 40	13	$11.2 \pm 1.6$	5.7

The number of readings at a time approaching 2 months after the onset of jaundice is, however, small. The Meulengracht test figures drop very gradually towards normal and because of that it is impossible to tell the exact date when the disturbance of which the test is an expression has subsided completely. The mean of 116 readings obtained during 26—40 days after appearance of jaundice is  $10.78 \pm 0.62$ . At this time we thus find a definite departure from the normal value obtained in healthy persons. The difference  $3.25 \pm 0.64$  is statistically significant.

The investigation shows that the disturbance brought about by the disease subsides very gradually and that signs of an impaired liver function can be traced during an unexpectedly long period after the disappearance of clinical symptoms. In this connection it should be kept in mind that normal weight has not been reattained after 5 weeks, that the suspension stability is still markedly lowered after 5 weeks and that urobilin is still present in the urine after 6 weeks.

A division of the material in a group of patients showing high



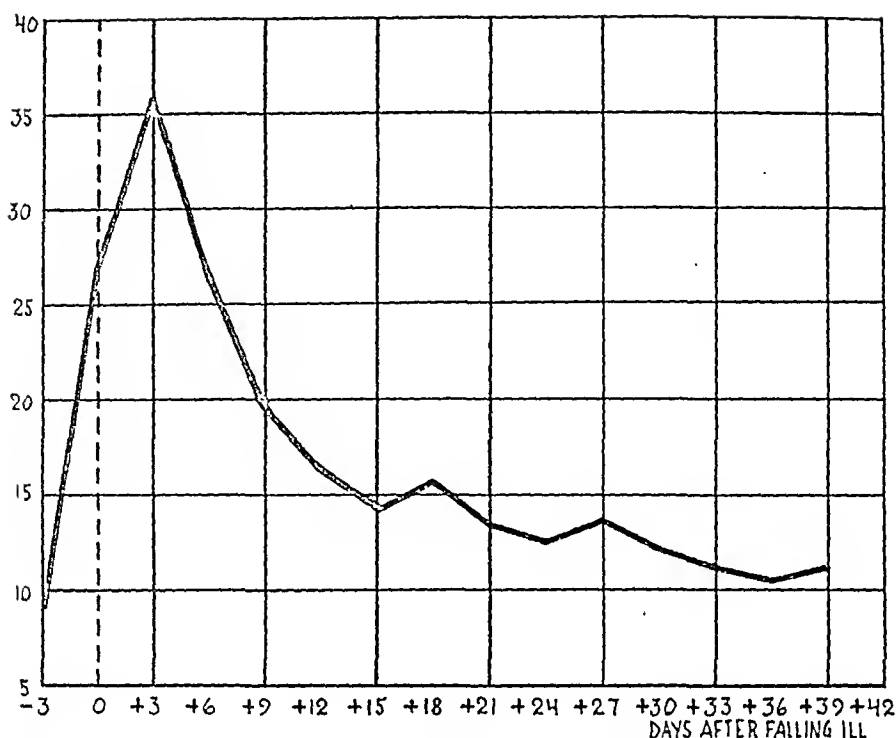


Fig. 11. Averages of the Meulengracht test readings on different days in 166 hepatitis cases in Hällnäs. 0 ist the day when the disease began.

values during the first six days (i. e. values in excess of the mean) and another group with lower values shows the return to the normal level to be slower where the initial values were high. See tables 20 and 21.

When comparing the Meulengracht values obtained during the earlier to those met with in the later part of the epidemic a statistically significant difference, namely  $12.8 \pm 3.9$  is found on the 9th—11th days, the earlier cases showing higher figures. The series of figures are by the way irregular on account of the smallness of the material. (See table 22.)

### The Hijman van den Bergh's test.

In the Umeå material the serumbilirubin quantities have been measured by the Hijman van den Bergh's method instead of by the Meulengracht test. The figures, however, show the same tendencies. In the hospital cases no tests have been carried out before the onset of jaundice, as has been the case with the sana-

TABLE 20.

Total number of cases who during the first 6 days of illness showed Meulengracht readings above respectively below the mean for the different days.

Day	Total number	Mean	Number above mean	Number below mean
0	28	26	15	13
1	38	27	16	22
2	22	34	12	10
3	22	35	8	14
4	8	43	2	6
5	3	30	1	2
6	10	30	6	4
Total	131	—	60	71

TABLE 21.

Means of Meulengracht tests in 2 groups; the first consisting of 60 cases with initial Meulengracht readings above the average during the first 6 days of illness, the second consisting of 71 cases with initial Meulengracht readings below the mean during the first 6 days of illness.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean for the different days.

Days	60 cases above the average		71 cases below the average	
	Number of cases	$M \pm \varepsilon(M)$	Number of cases	$M \pm \varepsilon(M)$
0—2	43	$39.0 \pm 1.5$	45	$18.4 \pm 0.92$
3—5	11	$59.4 \pm 5.7$	22	$24.5 \pm 2.2$
6—8	9	35.2	14	$13.5 \pm 3.0$
9—11	7	20.9	14	$11.9 \pm 1.1$
12—14	27	$15.6 \pm 1.4$	25	$13.5 \pm 3.7$
15—17	23	$19.0 \pm 3.4$	19	$11.4 \pm 1.4$
18—20	21	$20.0 \pm 5.7$	14	$12.4 \pm 1.9$
21—23	12	$11.6 \pm 1.2$	10	$10.4 \pm 1.6$
24—26	18	$13.9 \pm 0.99$	9	13.3
27—29	10	$12.3 \pm 1.4$	4	11.0
30—32	16	$13.3 \pm 2.0$	4	10.3
33—35	10	$9.6 \pm 0.75$	4	13.3
36—38	4	10.0	2	10.5
39—41	9	11.2	2	10.0
42—44	2	13.5	2	8.5
45—47	3	8.7	1	8.0
48—50	1	8.0	—	—
51—53	3	10.3	—	—
54—56	1	6.0	—	—
57—59	2	9.0	—	—

TABLE 22.

Average Meulengracht figures and standard deviations in the 83 first and 83 second cases of the epidemic respectively.  $n$  = number of observations.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.  $\sigma$  = standard deviation. Group I = the first 83 cases in chronological order. Group II = the later 83 cases in chronological order.

Days	Group I			Group II		
	$n$	$M \pm \varepsilon(M)$	$\sigma$	$n$	$M \pm \varepsilon(M)$	$\sigma$
--6--4	2	11.0	.	3	7.0	.
--3--1	4	9.6	.	6	21.5	.
0-2	34	29.0 $\pm$ 2.0	11.7	54	28.2 $\pm$ 1.9	14.1
3-5	19	38.8 $\pm$ 4.8	21.1	14	33.6 $\pm$ 5.9	22.2
6-8	16	23.1 $\pm$ 3.2	12.8	14	22.8 $\pm$ 6.2	23.3
9-11	22	22.6 $\pm$ 3.7	17.5	13	9.8 $\pm$ 1.3	4.8
12-14	29	15.8 $\pm$ 2.1	11.1	33	15.1 $\pm$ 2.9	16.5
15-17	34	13.4 $\pm$ 1.3	7.6	22	17.7 $\pm$ 3.6	17.0
18-20	30	18.0 $\pm$ 4.2	23.1	17	13.3 $\pm$ 1.8	7.5
21-23	16	10.8 $\pm$ 1.2	4.8	14	11.1 $\pm$ 1.1	4.1
24-26	23	12.65 $\pm$ 0.68	3.26	10	16.1 $\pm$ 3.2	10.3
27-29	10	12.8 $\pm$ 1.7	5.3	10	11.40 $\pm$ 0.90	2.84
30-32	16	12.3 $\pm$ 1.5	6.2	8	11.9	.
33-35	9	10.2	.	10	10.5 $\pm$ 1.0	3.3
36-38	5	10.0	.	3	10.0	.
39-41	8	11.6	.	6	9.3	.
42-44	2	8.5	.	2	13.5	.
45-47	3	8.7	.	1	8.0	.
48-50	1	8.0	.	1	6.0	.
51-53	1	13.0	.	2	9.0	.
54-56	2	7.0	.	—	—	—
57-59	1	10.0	.	1	8.0	.

torium patients, but the figures in tables 23 and 24 show high values already during the first days of illness which subsequently diminish gradually. Normal readings are reached after about 40 days, which corresponds fairly well to the results obtained by the Meulengracht method. The return to normal values corresponding to a gradually declining graph makes it difficult to decide when the normal level has been reached. See fig. 15 and tables 23-26. The direct tests convey the same impression as that given by the indirect tests. In the beginning of the disease we find more than 90 per cent positive readings. Subsequently the frequency of positive tests gradually decreases, but after one month we still find about half of the number to be »positives» or »traces». Later the number of observations becomes too small



Fig. 15. Averages for Hijman van den Bergh test (the vertical figures) on different days after taking ill in 149 hospital cases of uncomplicated hepatitis.

to permit of conclusions but not even after two months have all become negative.

### Galactose Tolerance Test.

In order to find out whether any signs of damage to the liver could be discovered during the advanced stages of the illness a number of galactose tolerance tests have been carried out on the hospital material at Umeå. In normal healthy people the galactose eliminated by the urine during the test generally does not exceed one gram. Between one and three grams is considered increasingly suspicious. Three grams mark the border line between the normal and the pathological. In other words, galactose amounts approaching three grams might under exceptional conditions be seen in normal persons, whereas an excretion in excess of three grams is looked upon as definitely indicative of liver insufficiency.

TABLE 23.

Serumbilirubin figures at 3 days intervals according to Hijman van den Bergh's indirekt test 1/200 000 in 149 cases of uncomplicated hepatitis treated at the Umeå hospital.  $n$  = number of observations.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Hijman v. Bergh's test	
	$n$	$M \pm \varepsilon(M)$
2—4	23	6.9 $\pm$ 1.5
5—7	44	6.90 $\pm$ 0.41
8—10	60	5.92 $\pm$ 0.43
11—13	52	4.50 $\pm$ 0.52
14—16	59	3.52 $\pm$ 0.44
17—19	55	2.50 $\pm$ 0.46
20—22	55	2.00 $\pm$ 0.30
23—25	51	1.48 $\pm$ 0.16
26—28	46	1.77 $\pm$ 0.24
29—31	44	2.15 $\pm$ 0.82
32—34	29	2.11 $\pm$ 0.24
35—37	30	2.80 $\pm$ 0.68
38—40	21	1.57 $\pm$ 0.30
41—43	18	1.55 $\pm$ 0.29
44—46	12	1.12 $\pm$ 0.14
47—52	15	2.51 $\pm$ 0.91
53—61	13	1.67 $\pm$ 0.43
62—73	11	2.00 $\pm$ 0.42
74—97	11	5.99 $\pm$ 3.50
98—136	6	0.98

TABLE 24.

Serumbilirubin figures at 6 days intervals according to Hijman van den Bergh's indirect tests 1/200 000 in 149 cases of uncomplicated hepatitis treated at the Umeå hospital.  $n$  = number of observations.

$M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Hijman v. Bergh's test	
	$n$	$M \pm \varepsilon(M)$
2—7	67	6.91 $\pm$ 0.57
8—13	112	5.26 $\pm$ 0.54
14—19	114	3.02 $\pm$ 0.32
20—25	106	1.74 $\pm$ 0.17
26—31	90	1.96 $\pm$ 0.41
32—37	59	2.46 $\pm$ 0.69
38—43	39	1.56 $\pm$ 0.21
44—52	27	1.89 $\pm$ 0.52
53—61	13	1.67 $\pm$ 0.43
62—97	22	3.99 $\pm$ 1.78
98—136	6	0.98

TABLE 25.

Distribution of Hijman van den Bergh's indirect test readings in 143 cases of uncomplicated hepatitis treated in the hospital at Umeå. N = the total number of observations in each period of 6 days. n = the number of observations in the respective groups.

Days after onset of illness	N	Groups of readings										Median
		0—1		1—3		3—6		6—9		9—		
		n	% of N	n	% of N	n	% of N	n	% of N	n	% of N	
2—7	67	1	1.5	7	10.4	19	28.4	25	37.3	15	22.4	6.8
8—13	112	2	1.8	34	30.4	30	26.8	26	23.2	20	17.9	5.1
14—19	114	17	14.9	59	51.8	23	20.2	10	8.8	5	4.4	2.4
20—25	106	33	31.1	60	56.6	9	8.5	3	2.8	1	0.9	1.7
26—31	90	37	41.1	45	50.0	4	4.4	2	2.2	2	2.2	1.4
32—37	59	21	35.6	27	45.8	6	10.2	3	5.1	2	3.4	1.6
38—43	39	9	23.1	26	66.7	3	7.7	1	2.6	—	—	1.8
44—52	27	10	37.0	15	55.6	—	—	1	3.7	1	3.7	1.5
53—61	13	3	23.1	8	61.5	2	15.4	—	—	—	—	2.0
62—97	22	2	9.1	14	63.6	4	18.2	—	—	2	9.1	2.4

TABLE 26.

Distribution of Hijman van den Bergh's direct test findings at 6 days intervals in 149 cases of uncomplicated hepatitis treated in the Umeå hospital. N = total number of observations during each period of 6 days. n = number of findings in respective groups.

Days after onset of illness	N	Hijman van den Bergh; direct							
		negative		faint trace		trace		positive	
		n	% of N	n	% of N	n	% of N	n	% of N
2—7	67	5	7.5	—	—	1	1.5	61	91.0
8—13	109	6	5.5	4	3.7	12	11.0	87	79.8
14—19	116	17	14.7	11	9.5	25	21.6	63	54.3
20—25	108	21	19.4	13	12.0	36	33.3	38	35.2
26—31	88	26	29.5	17	19.3	25	28.4	20	22.7
32—37	58	22	37.9	8	13.8	12	20.7	16	27.6
38—43	37	19	51.4	1	2.7	12	32.4	5	13.5
44—52	25	11	44.0	6	24.0	4	16.0	4	16.0
53—61	12	8	66.7	—	—	2	16.7	2	16.7
62—97	19	7	36.8	—	—	8	42.1	4	21.1

TABLE 27.

Average returns from Galactose tolerance tests in 131 cases of uncomplicated hepatitis from the hospital in Umeå at intervals of 12 days.  $n$  = number of observations.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Galactose excretion in grams during 24 hours after the administration of 40 grams	
	$n$	$M \pm \varepsilon(M)$
—16	4	0
17—29	70	$1.13 \pm 0.24$
30—42	57	$0.72 \pm 0.17$
43—55	21	$2.34 \pm 0.32$
56—	13	$1.00 \pm 0.41$

TABLE 28.

Distribution of positive Galactose tolerance tests in patients treated in the Umeå hospital for uncomplicated hepatitis at intervals of 12 days.  $n$  = number of observations.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Galactose excretion in grams during 24 hours after the administration of 40 grams	
	$n$	$M \pm \varepsilon(M)$
17—29	23	$3.44 \pm 0.47$
30—42	15	$2.74 \pm 0.25$
43—55	16	$3.07 \pm 0.18$
56—	5	2.60

The results of the tests have been tabulated in table 27. The average value is found to vary round one gram. The observed variations are due to chance and the small number of tests. The high average indicates that many patients have been included who excrete large amounts. Because of this the number of individuals showing a lowered tolerance have been tabulated. See table 28. In this table the negative (0 gram) tests were excluded. We now find averages of three grams which show definitely that numerous

TABLE 29.

Distribution of Galactose tolerance readings in excess of three and five grams respectively in uncomplicated hepatitis cases from the Umeå hospital at intervals of 12 days.  $P \pm \varepsilon(P)$  = per cent of total number of observations (=N)  $\pm$  standard error of the percentage.

Days after onset of illness	Galactose excretion in grams during 24 hours after the administration of 40 grams				
	N	Number of observations exceeding 3 grams		Number of observations exceeding 5 grams	
		Absolute numbers	$P \pm \varepsilon(P)$	Absolute numbers	$P \pm \varepsilon(P)$
—16	4	—	—	—	—
17—29	70	10	$14.3 \pm 4.2$	5	$7.2 \pm 3.1$
30—42	57	5	$8.8 \pm 3.7$	—	—
43—55	21	4	$19.1 \pm 8.6$	1	$4.8 \pm 4.6$
56—	13	1	$7.7 \pm 7.4$	—	—

patients have a lowered galactose tolerance. In order to demonstrate this even more clearly, the number of individuals with values in excess of three and five grams respectively have been registered in table 29 from which it will be seen that quite a number of cases exceed these limits. During the period 17 to 55 days after falling ill we thus find 12.8 % of the cases having definitely pathological values. The pathologically lowered tolerance seems to be more frequent during the 3rd to 4th weeks than later.

### Bile pigments in urine.

Urine has been tested for *urobilinogen* during the period of jaundice and some days before. The test is positive to a comparatively large extent already before jaundice becomes manifest. Subsequently the number of positive test drops and two weeks after the appearance of jaundice the numbers of positive tests are comparatively few. See fig. 16.

The diagram has been constructed in the following way.

The positive values have been plotted in the first instance (viz. 53.1 % during the last 6 days before onset). From the point thus obtained the percentage of 'traces's' is marked (being 28.1 % during the same period).



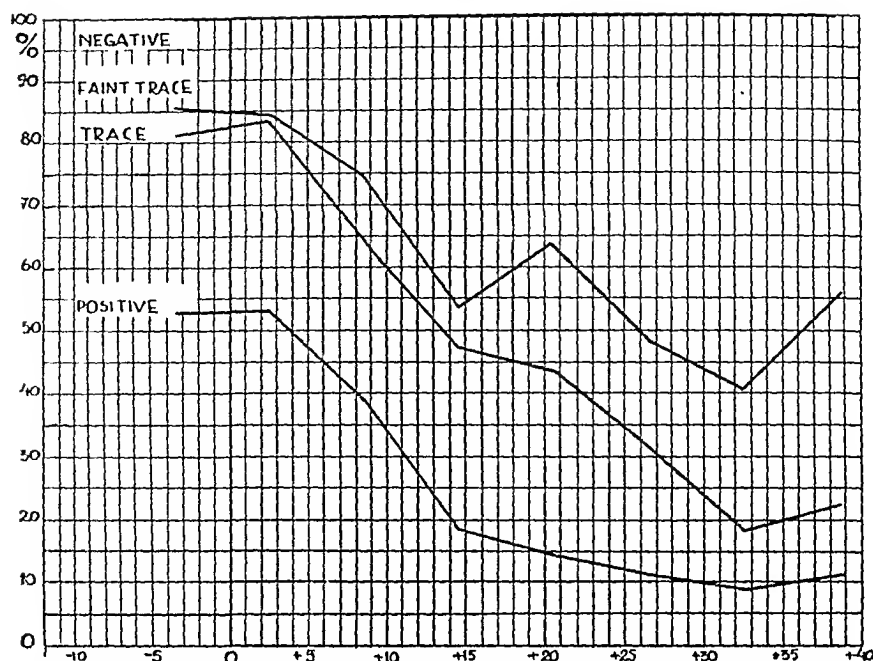


Fig. 16. Distribution in percentage of positive and negative urobilinogen tests as well as of tests interpreted as being »trace» or »faint trace» on different days before and after the beginning of the disease. (On every day the sum of the tests must be one hundred.)

'Faint traces' come next (4.7 %) and finally the percentage of negative tests (14.1 %). The sum thus makes 100 % and represents the distance between the abscissa and the upper limit of the diagram.

TABLE 30.

Results of urobilinogen tests in 166 hepatitis cases at the Hällnäs sanatorium. N = total number of tests. n = number of observations.

$P \pm \varepsilon(P)$  = per cent  $\pm$  standard error of the percentage.

Days	N	Negative		Faint trace		Trace		Positive	
		n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$
Groups I + II.									
— 6 — — 1	64	9	14.1 $\pm$ 4.4	3	4.7 $\pm$ 2.6	18	28.1 $\pm$ 5.6	34	53.1 $\pm$ 6.2
0—5	186	29	15.6 $\pm$ 2.7	2	1.1 $\pm$ 0.76	56	30.1 $\pm$ 3.4	99	53.2 $\pm$ 3.7
6—11	143	36	25.2 $\pm$ 3.6	15	10.5 $\pm$ 2.6	36	25.2 $\pm$ 3.6	56	39.1 $\pm$ 4.1
12—17	119	55	46.2 $\pm$ 4.6	8	6.7 $\pm$ 2.3	34	28.6 $\pm$ 4.1	22	18.5 $\pm$ 3.6
18—23	69	25	36.2 $\pm$ 5.8	14	20.3 $\pm$ 4.8	20	29.0 $\pm$ 5.5	10	14.5 $\pm$ 4.2
24—29	35	18	51.5 $\pm$ 8.4	6	17.1 $\pm$ 6.4	7	20.0 $\pm$ 6.8	4	11.4 $\pm$ 5.4
30—35	22	13	59.1 $\pm$ 10.5	5	22.7 $\pm$ 8.9	2	9.1 $\pm$ 6.1	2	9.1 $\pm$ 6.1
36—41	9	4	44.5	3	33.3	1	11.1	1	11.1
42—47	2	—	—	1	50.0	1	50.0	—	—

Corresponding displacements are observed regarding the frequency of patients with negative tests and individuals showing traces or faint traces.

The *iodine test* also shows similar displacements. Positive reactions, however, only become numerous a few days after the beginning of jaundice, thus indicating the urobilinogen test to be more sensitive in the preicteric stage. In contrast the percentage of positive iodine tests is higher than that of the Schlesinger tests, or as much as 84 %. After 3—4 weeks the proportion of positive tests is low. See table 31.

TABLE 31.

Results of iodine tests in 166 hepatitis cases at the sanatorium in Hällnäs. N=total number of tests. n=number of observations.  $P \pm \varepsilon(P)$ =per cent  $\pm$  standard error of the percentage.

Days	N	Negative		Faint trace		Trace		Positive	
		n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$	n	$P \pm \varepsilon(P)$
-18--13	3	3	100.0	—	—	—	—	—	—
-12--7	12	12	100.0	—	—	—	—	—	—
-6--1	91	39	$42.8 \pm 5.2$	1	$1.1 \pm 1.1$	17	$18.7 \pm 4.1$	34	$37.4 \pm 5.1$
0-5	182	12	$6.6 \pm 1.8$	—	—	16	$8.8 \pm 3.0$	154	$84.6 \pm 2.7$
6-11	147	50	$34.0 \pm 3.9$	—	—	40	$27.2 \pm 3.7$	57	$38.8 \pm 4.0$
12-17	119	78	$65.5 \pm 4.4$	—	—	19	$16.0 \pm 3.4$	22	$18.5 \pm 3.6$
18-23	68	48	$70.5 \pm 5.5$	1	$1.5 \pm 1.5$	14	$20.6 \pm 4.9$	5	$7.4 \pm 3.2$
24-29	36	30	$83.3 \pm 6.2$	—	—	4	$11.1 \pm 5.2$	2	$5.6 \pm 3.8$
30-35	22	17	$77.3 \pm 8.9$	—	—	4	$18.2 \pm 8.2$	1	$4.5 \pm 6.6$
36-41	9	9	100.0	—	—	—	—	—	—
42-47	2	2	100.0	—	—	—	—	—	—

The percentages of individuals with respectively 'negative' 'trace' and 'faint trace' reactions run parallel. *Urobilin tests* show a graph similar to that of urobilinogen in as much as the reactions become positive a few days before jaundice is manifest and fades away in 2—3 weeks. The positive reactions, however, never attain the same high frequencies. In contrast the number of tests classified as 'trace' and 'faint trace' is very high. Uncertainty is greater when estimating urobilin than urobilinogen, urobilin more frequently being considered to be present as 'trace' only. See table 32.

A comparison of the readings by the various tests for bile pigments in the urine has also been carried out between the earlier and later halves of the patients. As, however, significant differences were not noted, the figures have not been included.

TABLE 32.

Findings by urobilin tests in 166 hepatitis cases at the Hällnäs sanatorium.  $N$  = total number of tests.  $n$  = number of observations.  $P \pm \epsilon(P)$  = per cent  $\pm$  standard error of the percentage.

Days	N	Negative		Faint trace		Trace		Positive	
		n	$P \pm \epsilon(P)$	n	$P \pm \epsilon(P)$	n	$P \pm \epsilon(P)$	n	$P \pm \epsilon(P)$
--12--7	6	—	—	3	50.0	3	50.0	—	—
--6--1	65	2	$3.1 \pm 2.1$	3	$4.6 \pm 2.6$	38	$58.5 \pm 6.1$	22	$33.8 \pm 5.9$
0-5	186	4	$2.2 \pm 1.1$	13	$7.0 \pm 1.9$	91	$48.9 \pm 3.7$	78	$41.9 \pm 3.6$
6-11	146	10	$6.8 \pm 2.1$	21	$14.4 \pm 2.9$	67	$45.9 \pm 4.1$	48	$32.9 \pm 3.9$
12-17	121	14	$11.6 \pm 2.9$	44	$36.4 \pm 4.4$	32	$26.4 \pm 4.0$	31	$25.6 \pm 4.0$
18-23	45	5	$11.1 \pm 4.7$	17	$37.8 \pm 7.2$	17	$37.8 \pm 7.2$	6	$13.3 \pm 5.1$
24-29	37	4	$10.8 \pm 5.1$	19	$51.4 \pm 8.2$	7	$18.9 \pm 6.4$	7	$18.9 \pm 6.4$
30-35	22	3	$13.6 \pm 7.3$	11	$50.0 \pm 10.7$	6	$27.3 \pm 9.5$	2	$9.1 \pm 6.1$
36-41	10	3	30.0	5	50.0	1	10.0	1	10.0
42-47	2	—	—	1	50.0	—	—	1	50.0

TABLE 33.

Hammarsten tests in hepatitis cases at the Hällnäs sanatorium.  $N$  = total number of tests.  $n$  = number of observations. Group I = the first 83 cases in chronological order. Group II = the later 83 cases in chronological order.

Days	N	Negative		Faint trace		Trace		Positive	
		n	%	n	%	n	%	n	%
Group I.									
- 6- - - 1	5	4	80.0	—	—	—	—	1	20.0
0-5	10	—	—	—	—	1	10.0	9	90.0
6-11	1	—	—	—	—	1	100.0	—	—
12-17	—	—	—	—	—	—	—	—	—
Group II.									
- 6- - - 1	2	2	100.0	—	—	—	—	—	—
0-5	2	—	—	—	—	1	50.0	1	50.0
6-11	—	—	—	—	—	—	—	—	—
12-17	1	1	100.0	—	—	—	—	—	—
Groups I + II.									
- 6- - - 1	7	6	85.7	—	—	—	—	1	14.3
0-5	12	—	—	—	—	2	16.7	10	83.3
6-11	1	—	—	—	—	1	100.0	—	—
12-17	1	1	100.0	—	—	—	—	—	—

### Duration of icteric stage.

Regarding the time during which a disturbance of the distribution of bile pigments in the body can be shown, i. e. the icteric stage, urobilinogen tests indicate this period to last slightly more than a fortnight, whereas it extends to 3 weeks if determined by the results of resp. the urobilin and iodine tests. The Meulengracht tests too suggests an icteric stage of 3 weeks. Jaundice thus can be said to be a phenomenon which occurs suddenly and afterwards fades away gradually. Hence it is difficult to establish a fixed date when jaundice can be considered to have subsided. To judge by the chemical reactions the average duration of the icteric stage should hardly exceed 3 weeks. One is inclined to believe that the time is shorter still if determined by clinical observation, provided that the observer is not abnormally colour sensitive.

When, however, there is the question of gradually fading colour shades the definition of a limit becomes far more difficult by inspection of the patient than by the reading of chemical tests where a certain objectivity is arrived at.

### Blood Status.

The hospital patients in Umeå have had their blood examined, the tests being carried out only after the outbreak of illness. Accordingly we have no information regarding the proportions of the different blood elements before that date. As probable average normal values from which to depart when discussing the significance of the tabulated findings we have adopted 4,423 million erythrocytes and 85.53 per cent hæmoglobin.

These figures have been adapted from those given in ODIN's investigation by allowing for the way in which the observations have been found to be distributed between the sexes in the actual material.

The number of *erythrocytes* during the 2nd—4th days of illness reaches 4.8 millions. Three by four weeks later the figure found is 4.5 millions. The difference between 2nd—4th and the 17th—31st days being  $0.47 \pm 0.15$ , the displacement is statistically proven. This indicates a slight decrease in the number of erythrocytes.

Two interpretations of the figures appear possible: the alterations on the one hand might have taken place in the plasma and

TABLE 34.

Average number of erythrocytes and average hæmoglobin-figures in 146 cases of uncomplicated hepatitis at the Umeå hospital at three days intervals.  $n$  = number of observations.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Million erythrocytes		Hæmoglobin per centage according to Autenricht		Colour index
	$n$	$M \pm \varepsilon(M)$	$n$	$M \pm \varepsilon(M)$	
2—4	22	$4.81 \pm 0.12$	22	$91.5 \pm 2.5$	1.051
5—7	43	$4.762 \pm 0.075$	43	$88.6 \pm 1.5$	1.075
8—10	45	$4.724 \pm 0.080$	46	$89.7 \pm 1.5$	1.053
11—13	15	$4.47 \pm 0.12$	15	$83.5 \pm 2.4$	1.071
14—16	20	$4.53 \pm 0.10$	20	$86.3 \pm 2.3$	1.050
17—31	23	$4.341 \pm 0.095$	24	$80.3 \pm 1.5$	1.081
32—62	18	$4.40 \pm 0.11$	18	$78.9 \pm 2.3$	1.115
63—113	6	4.20	6	78.8	1.066

represent a phenomenon of desiccation, on the other hand the observed changes might refer to a decrease in numbers of the red blood cells. Theoretically of course both mechanisms might be at work simultaneously. On the face of it, desiccation appears to be more likely than anemia because considerable loss of fluid through persistent vomiting and consequent difficulties in retaining drink, forms part of the typical course of the disease. This interpretation is supported by the fact that the number of the erythrocytes does not rise during the 30th—60th days. If the cause had been anemia one might possibly have expected a reparative reaction to appear during this period.

The figures representing *hæmoglobin*, values show corresponding fluctuations; that is slightly raised readings during the first days of illness and significant decrease to constant values during the subsequent weeks. The figures relating to *colour index* included in the table have no other interest than to show this to remain constant. There was no reason to expect anything else.

The number of *white blood cells* show a slight increase about a fortnight after the onset. See table 35. The difference, being  $1.36 \pm 0.46$  is statistically proven, but is of so insignificant a magnitude as to be of slight interest only. No values being available from the time prior to onset it is impossible to form a definite opinion. If the displacement is due to a relative leucopenia in the beginning or a leucocytosis at the end of the disease can not be decided.

TABLE 35.

Average white blood cell counts in 145 uncomplicated cases of hepatitis treated at the Umeå hospital at intervals of three days.  $n$  = number of observations.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	n	Polynuclear white cells in thousands	Mononuclear white cells in thousands		Total number of white cells in thousands = N
		$M \pm \epsilon(M)$	$M \pm \epsilon(M)$	% of N	$M \pm \epsilon(M)$
2-4	21	$3.40 \pm 0.28$	$1.533 \pm 0.075$	31.0	$4.94 \pm 0.29$
5-7	42	$3.88 \pm 0.19$	$1.91 \pm 0.12$	33.0	$5.79 \pm 0.22$
8-10	45	$3.83 \pm 0.17$	$1.780 \pm 0.086$	31.7	$5.61 \pm 0.19$
11-13	15	$3.61 \pm 0.25$	$1.85 \pm 0.13$	33.9	$5.46 \pm 0.28$
14-16	22	$4.45 \pm 0.32$	$1.85 \pm 0.17$	29.4	$6.30 \pm 0.36$
17-31	11	$3.81 \pm 0.20$	$1.66 \pm 0.19$	30.3	$5.47 \pm 0.28$
32-113	13	$3.88 \pm 0.78$	$1.88 \pm 0.13$	32.6	$5.76 \pm 0.79$
2-113	169	3.85	1.80	31.7	5.67

TABLE 36.

Average figures from differential counts of white blood cells in 39 cases of uncomplicated hepatitis treated at the Umeå hospital. N = neutrophile leucocytes. E = eosinophile leucocytes. B = basophile leucocytes. L = lymphocytes. StM = large mononuclear cells.  $n$  = number of observations.  $M \pm \epsilon(M)$  = mean  $\pm$  standard error of the mean.

Days after onset of illness	Differential count					
	n	$M \pm \epsilon(M)$				
		N	E	B	L	StM
2-9	23	$59.0 \pm 2.6$	$1.50 \pm 0.35$	$0.130 \pm 0.065$	$33.6 \pm 2.3$	$5.85 \pm 0.52$
10-17	12	$62.4 \pm 2.6$	$0.92 \pm 0.25$	0	$31.2 \pm 2.2$	$5.54 \pm 0.75$
18-	8	58.6	2.4	0.1	33.8	4.8

The figures regarding the subdivision of the white blood cells in *poly- and mononuclear cells* have also been tabulated. Here we do not find any displacement in their quantitative relationship, both categories accordingly increasing slightly in numbers during the first fortnight of the illness.

*Differential counts* have been made in a small number of cases. Figures are given for the sake of completeness only, they show, however, no departures from the normal.

## Urine.

Records of urine examinations are available from 92 patients of the Hällnäs material. Transient traces of albumen have been found in 6 instances, accompanied with the appearance of a few red and white cells in the sediments. In no case could any serious or lasting influence on the kidneys be demonstrated. A positive Diazo test was noted for the first time during the disease in one instance only. Glycosuria has not been observed. The two diabetics treated at the sanatorium did not catch hepatitis. In the hospital material we find only one diabetic.

## Neurological.

Cerebral symptoms have not been registered in any case in the Hällnäs material. Bradycardia, considered as a sign of biliar irritation of the oblongata is said to be a conspicuous feature in certain forms of jaundice.

It has therefore been considered desirable to investigate whether any slowing down of the pulse rate could be found in epidemic hepatitis. The tubercular patients with their frequently accelerated pulse rates were a priori regarded as unsuitable subjects for this study. It was found in addition that no pulse graphs had been recorded. One had to turn to the hospital patients in order to form an opinion. Pulse rates and temperatures are at the Umeå hospital entered on the same charts,  $36^{\circ}\text{C}$ . corresponding to 60 pulse beats per minute,  $37^{\circ}$  to 70,  $38^{\circ}$  to 80 and so on. If the divergencies between the two curves did not exceed 5 units (i. e.  $0.5^{\circ}$  temperature or 5 beats pr. min.) the pulse graph was considered not to be displaced ( $P = T$ ). Slowing down in excess of the said amount has been interpreted as bradycardia ( $P < T$ ), tachycardia being presented by the inverse displacement. This might be considered a rather rough and ready method but it is accurate enough to convey a general idea.

Out of 146 examined charts 135 showed perfect agreement between temperature and pulse, whereas tachycardia had been registered in 6 and bradycardia in 5 instances. A slowing of the heart beat accordingly can not be said to be characteristic of the disease.

**Relapses** have not been observed.

### Treatment.

As has been already set forth the patients have been confined to bed during varying lengths of time.

During the first week or fortnight and otherwise as long as the Menlengracht values exceeded 20 a lacto-cereal diet was served, whereafter fish and small amounts of butter were added. When the Menlengracht tests had dropped below 10, the patients returned to the standard fare of the sanatorium.

Beyond symptomatic treatment of various subjective discomforts no specific therapy was attempted.

### Prognosis.

11 of the tubercular patients who contracted hepatitis died during the year of 1941. According to the opinion of the physicians the deceased had been in a bad state already at the onset of hepatitis and the deterioration had not been accelerated in consequence of the complication. Obviously, however, an ailment affecting the alimentary tract and entailing grave lesions of the liver must of necessity be expected to render nutrition more difficult and might lower the patients resistance. Anyhow, a comparison of the mortality rate in 1941 with that recorded in previous years during which the number of patients have been about the same and the principles for admittance and discharge have been unaltered might be expected to illustrate the question:

Year	Number of patients	Number of deaths
1937	333	79
1938	333	95
1939	340	63
1940	340	69
1941	360	66

The mortality figures thus do not seem to indicate a decisively unfavourable influence on the course of the tubercular disease.

Among my 147 hospital patients two have died from their hepatitis (representing a mortality rate of 1.4 per cent). As presumably in the first place only the more severe cases have been admitted to hospital treatment a certain amount of selection has taken place. The mortality figure in my hospital material accordingly ought to be appreciably higher than in patients



treated in their homes. What the total hepatitis mortality has been during the time under review is not known.

It has been shown in the discussion on the duration of jaundice that a disturbance in the distribution of bile pigments can be demonstrated by various tests for weeks and months after the disappearance of subjective discomfort or jaundice discernible to the eye. Even if a *restitutio ad integrum* ought to be the rule a certain number of cases possibly sustain permanent damage to their liver tissue which eventually is replaced by fibrous proliferation of varying intensity culminating in the final cirrhotic stages. To what extent a past attack of hepatitis can be discovered in the records of cirrhosis cases is outside the scope of the present work and has moreover been exhaustively investigated by Bergstrand. A careful following up of the present numerous hepatitis cases at regular intervals ought, however, to enlarge our knowledge and enable us in the future to forecast with greater confidence the ultimate chances of recovery. The analysis of the Meulengracht tests in Hällnäs has proven that high initial readings predict drawn out disturbances and one must accordingly admit that this symptom has a certain prognostic value. An extended use of quantitative estimates of citric acid and phosphatas in serum would certainly enable us to discover the permanent and progressive nature of a pathological process at an early stage.

### Preventive measures.

Experiences from the epidemics of hepatitis in the county of Västerbotten indicate the line of action which should be taken in order to be on the safe side in combating outbreaks of the disease.

Any local accumulation of simultaneous cases whether in a family, school or institution should direct the attention of the medical officer to the water supply. In this country the drinking facilities in rural schools are often particularly unsatisfactory. The primitive arrangement — a pail of water in one corner of the class room and a scoop used both as ladle and drinking eup by all the children — is still very common. Many of the so called »Sanitary» patented drinking fountains boasted by some schools are almost equally unhygienic in as much as the mouthpieces are not effectively protected against contact with the lips. The source of water often leaves much to be desired. Good wells, yielding unimpeachable subsoil water are still rare exceptions. A sanitary inspection of wells complemented by bacteriological

examinations of the water should form part of the routine. Advice how to repair defects should be tendered to the landlord and the public health committee should be instructed to supervise the carrying out of enjoined measures.

There is no call for the closing of schools or prohibition against assemblies, neither need any particular precautions be taken for the isolation of cases in hospitals or barracks. Ordinary cleanliness and some caution in the handling of soiled objects ought to suffice. It should also be insisted on that the patient should be given a bed of his own.

The role played by rodent vectors of the contagion not being established, an epidemic of hepatitis unfortunately does not, at the present stage of our knowledge, provide a scientifically valid pretext for a maybe otherwise desirable deratisation campaign.

Human blood has of late found an ever increasing use for the production of convalescent serums and for blood transfusions. That such a utilization is fraught with certain dangers show the epidemics of hepatitis caused by inoculations of serums contaminated by hepatitis virus mentioned in the review of the literature. Great care should accordingly be exercised when collecting blood for therapeutic purposes. Areas where hepatitis is rampant had better be avoided and the blood collectors should be constrained to elicit information whether would be donors have suffered from jaundice recently. As we have no means of knowing during how long a time the virus might remain in the blood the safest way would be to reject all who have had the disease. Subsequently the state of health of the donor should be watched with an eye to hepatitis and serum or blood should not be issued to the profession until the time of incubation has passed without any signs of the disease appearing in the donor.

## Summary.

It has been pointed out in a survey of the literature that most of the authors consider epidemic hepatitis to be transmitted by contact. Certain epidemics, however, suggest the possibility of a spread by ingestion in the same way as enteric fevers. The mode of propagation, thus, cannot be considered as definitely settled. Possibly we may have to deal with different diseases, which, though clinically similar are transmitted in different ways. As regards the *epidemiology* in my material it has been possible to show the following:

1) During an outbreak in a sanatorium (Hällnäs) in the county of Västerbotten 178 cases occurred. The water conduit of the sanatorium had become polluted from a defective drain. 34 days after the infected well had been excluded, the epidemic came to an end, a few odd cases only occurring during the following 18 days. This corresponds to the time of incubation and indicates infection by water. Some other outbreaks in Västerbotten also seem to suggest transmission by water. The principles of preventive measures are discussed and the importance of improved water hygiene underlined in this connection.

2) Among 188 persons who had joined the sanatorium population either as patients or personnel after the exclusion of the well, no case of the disease occurred although the new arrivals came into contact with a large number of unisolated cases. This indicates definitely that the disease with which we have to deal here is not transmitted by contact.

3) The time of incubation computed by statistical analysis of the sanatorium material has been found to range between 34 and 52 days. In 10 actual cases an incubation time from 28 to 43 days was found, the figures being in fairly good agreement with those statistically deduced.

4) The susceptibility among those exposed to water borne infection works out at 32 %, no difference being found between men and women. Children have not shown themselves particularly

liable to contract the disease, but their number in the present material is not large and accordingly does not permit of any definite conclusions.

Regarding the *clinical* aspects of the disease the following results might be noted:

5) The preicteric stage has been found to last on an average 6 days, varying in length between only one or two days and upwards of a fortnight; the longest time observed in my material being 16 days.

6) In order to form a correct estimate of the significance of the readings obtained by the Meulengracht test, an investigation into its variations in normal persons has been carried out. The average worked out at  $7.53 \pm 0.14$  and the standard deviation at 2.12. The range of variation extends from 1.2 to 13.9.

Jaundice, as indicated by the Sernbilirubin tests devised by Meulengracht and Hijman van den Bergh has been found to last on an average between 4 and 6 weeks, during which time bile pigments have been shown by the Iodine and Schlessinger tests to be present in the urine also. In as far as the Galactose tolerance test gives an idea about the functional state of the liver, an analysis of the results of this test in a number of hospital (Umeå) patients seems to indicate an impaired liver function as long as 55 days after the onset of the illness in 13 % of the cases.

7) The general repercussions of the disease as indicated by such circumstances as the length of time during which it has been found necessary to keep the patients in bed; the loss of weight; the rise in temperature and the lowered suspension stability of the erythrocytes, have been analysed. The bed treatment has on an average lasted 4 weeks and by that time the loss of weight has been made good. The temperature has been found to rise coinciding with the taking ill of the patient and attains its maximum during the first few days of the illness, then to drop slowly to normal in three weeks. The beginning of jaundice is not accompanied by a rise of temperature. The suspension stability of the erythrocytes is also affected by the disease, the reaction, however, apparently taking different courses in uncomplicated cases and in such patients as are in advance suffering from tuberculosis. In the latter category we meet with a maximum decrease after about 4 weeks and a return to the values departed from about a month later, whereas the uncomplicated cases show a continuously decreased stability culminating after two months.

8) The general impression of the physicians in charge of the sanatorium has been that those who caught the disease in the beginning of the epidemic suffered more severely than those who took ill later. This has been borne out by statistical analysis of such phenomena as the length of the preicteric stage, the rise in temperature, the disturbance of bile pigments and the decreased suspension stability, in the earlier half and the later half of the patients.

9) With regard to the subjective symptoms those from the digestive tract have predominated, nausea and vomiting being registered in 72 % of the cases. An obstinate constipation especially after the beginning of jaundice has been complained of in 35 %.

10) An investigation into the composition of the blood has only revealed slight disturbances (increased number of erythrocytes) which may be taken as a sign of temporary desiccation. The white blood cell counts showed significant though very moderate fluctuations, but no real leucopenia or leucocytosis have been observed. The disease has been found not to affect the kidneys to any appreciable or serious extent. As a rule the relation between pulse beat frequency and body temperature has not been disturbed; bradycardia and tachycardia being equally infrequent.

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The resistance in pieces of 15 per cent gelatin only was tested, and the values compared with corresponding values for 15 per cent gelatin + barium sulphate. It is found that the former has a somewhat lower resistance. The difference in the resistance for gelatin with barium sulphate is  $0.112 \pm 0.024$  kg.

The resistance of the material when kept has also been tested. After 4 days, 15 per cent gelatin with barium sulphate shows an increased resistance, and the difference, compared with samples of fresh pieces, is  $0.200 \pm 0.021$  kg.

The difference in resistance in hardening for 12, 24 and 48 hours shows only small differences, which are not statistically significant. On the other hand, the values for the differences show an increase of resistance in comparison with mildly hardened, standard-hardened and strongly hardened pieces.

Investigation of the test portions show that, as regards the compressibility and resistance of the material, small but statistically significant differences can be shown, above all as regards gelatin content and strength of formalin at hardening. On the other hand, the time for hardening (12—48 hours) and the keeping up to 4 days have played a smaller part. The test material would seem to possess suitable properties, since it remains fairly constant when kept, and since, above all, the values for the variation of test portions prepared in a standardized way, are small.

A further advantage is that, with the methods of testing the compressibility and resistance used here, it is possible to control the nature of the material. The mass-produced gelatin used can, of course, be suspected of variation, and the methods and values given provide a check in this direction. On account of the difficulties in procuring material, however, it has not been possible at this time to test gelatin from different factories.

With regard to the values obtained, it may finally be said that test portions with varying gelatin content showed moderate differences, but that 15 per cent gelatin rather seems to have the most constant character, i. e. to show the least variability in the portions as regards compressibility and resistance.

For the tests a material of 15 per cent gelatin and 5 per cent barium sulphate, hardened 24 hours in a solution of 50 g. of 36—38 per cent formalin and 350 g. of water, was used. The test portions were washed in water for 12 hours. The weight was 11.4 g. and the volume 10.6 c. cm. for grown-up persons. For children the weight was 7.9 g. and the volume 7.1 c. cm.

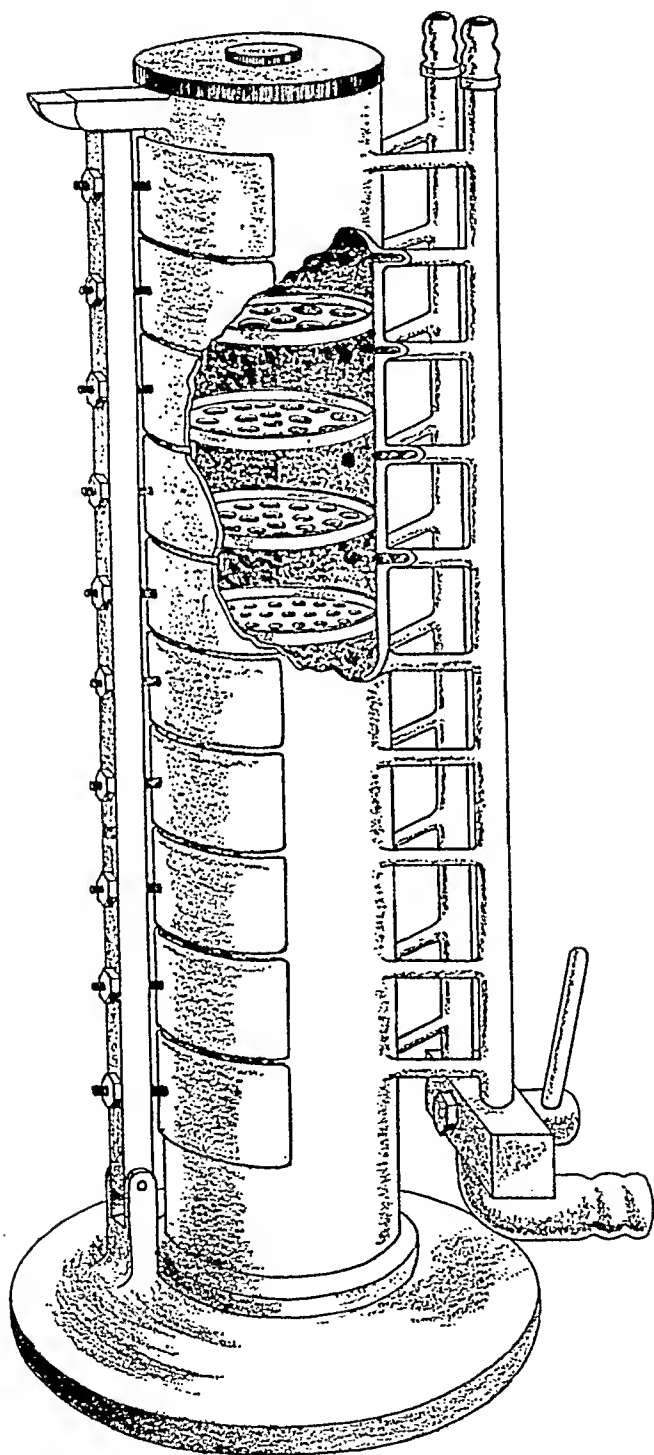


Fig. 3. Apparatus for straining.

TABLE 28.

Number of contacts of teeth in older women, divided into groups with sets of teeth in varying condition. Regarding class limits, see Table 17. Theoretical class midpoint =  $T$ .  $n$  = number of persons.  $M \pm \varepsilon(M)$  = mean  $\pm$  standard error.  $\sigma$  = standard deviation.

Set of teeth	$n$	$T$	$M \pm \varepsilon(M)$	$\sigma$
Grinding teeth				
Group I: extremely good	10	21	$18.90 \pm 0.46$	1.45
» II: good	17	13	$12.18 \pm 0.27$	1.13
» III: bad	12	9	$8.67 \pm 0.19$	0.65
» IV: extremely bad	11	3.5	$4.55 \pm 0.53$	1.75
Cutting teeth				
Group I: extremely good	10	—	$4.90 \pm 0.48$	1.52
» II: good	17	—	$5.71 \pm 0.11$	0.47
» III: bad	12	—	$5.25 \pm 0.46$	1.60
» IV: extremely bad	11	—	$5.18 \pm 0.33$	1.08

in these women was such as to compel their being referred to group IV, i. e. extremely bad sets of teeth. It was further found that the grinder occlusion contacts were missing or else so few that the material did not lend itself to an investigation of the mastication effectivity. Only a few individuals could be used.

The investigation material had therefore to be sought elsewhere. At factories and other places of work, there proved to be great difficulties in getting older women with their own teeth for an investigation. The material that has been tested with regard to masticatory powers is mainly taken from the author's private practice.

The older women investigated belonged, as a rule, to the more well-to-do classes, and consisted of persons who had looked after their teeth. The number of teeth was comparatively good, and displayed small differences compared with the number in adult women, in spite of the difference in the average age between the two materials. Incisors were found to practically the whole of the calculated number, being absent in 3.1 per cent, grinders except for wisdom teeth to about three fourths or 72.5 per cent and wisdom teeth to about one fourth or 22.9 per cent.

The material is divided into four groups within the same limits for the point values as were used for adult men. A survey of

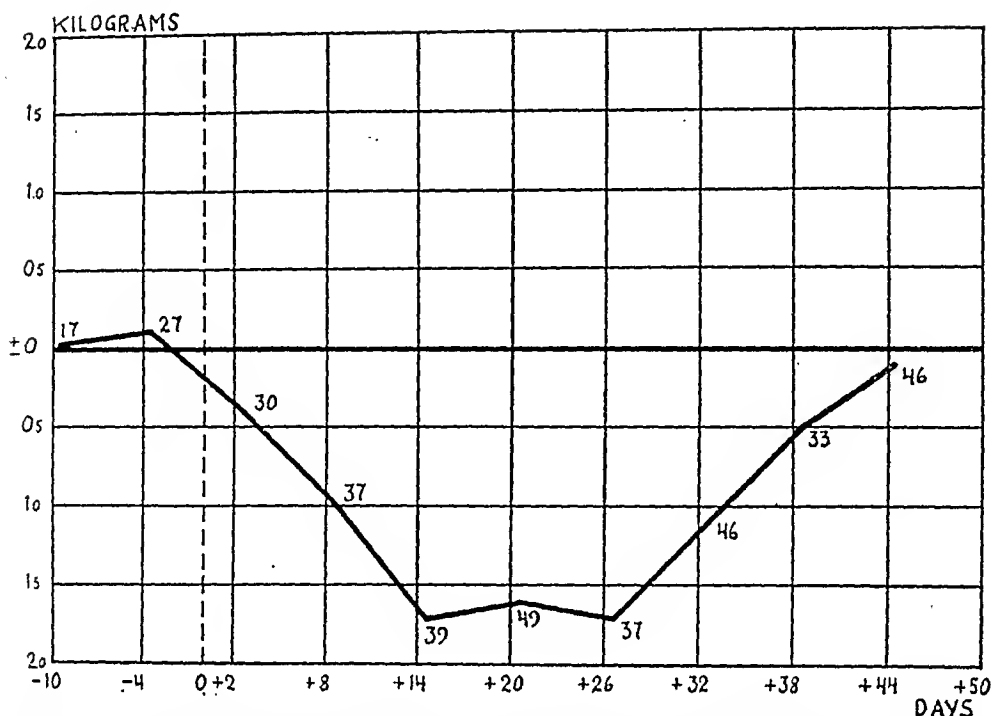


Fig. 9. Average loss in weights at 6 days intervals after falling ill in 113 sanatorium patients suffering from hepatitis.

through successive hosts. On this occasion the development apparently has been in the opposite direction. Accordingly it only remains to explain the observed displacement by assuming that in the beginning of this as in other epidemics those most susceptible might possibly contract the disease first and accordingly develop more pronounced symptoms. See fig. 10 and table 14.

### Suspension stability of the erythrocytes.

Alterations in the suspension stability of the erythrocytes reflect a general reaction much in the same way as do changes of temperature and thus are worthy of attention. The material used is formed by tested tubercular patients and no selection has been made. Thus it is to be expected that the suspension stability is more or less lowered already before their falling ill with hepatitis. Accordingly in this calculation the differences from the last values available before the onset of hepatitis have been computed.

If it had been possible to tell in advance if and when a person would contract hepatitis the suspension stability could have been tested at exactly the same date in all cases. In reality, however, the date must vary, and on an average the value of departure